PSJ2 Exh 43

IND/NDA

4795

Purdue Pharma L.P.

100 CONNECTICUT AVENUE, NORWALK, CONNECTICUT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

January 11, 1996

RESPONSE TO
PROMOTIONAL QUESTIONS

TWO COPIES SUBMITTED
UNDER SEPARATE COVER
TO ANESTHETIC/CRITICAL
CARE & ABUSE DRUGS

ltr follows this one

Diane Schnitzler
Division of Drug Marketing, Advertising and Communications
Food and Drug Administration
HFD-40, Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: OXYCODONE HYDROCHLORIDE
NDA #20-553

Dear Ms. Schnitzler:

Reference is made to our New Drug Application, NDA #20-553 for OxyContin™ Controlled-Release Tablets, filed December 28, 1994 and approved December 21, 1995. Reference is also made to our promotional launch items filed October 12, 1995 and November 30, 1995; and to a December 20, 1995 letter received by us from the Division of Drug Marketing, Advertising and Promotion (DDMAC) which commented on the submitted launch items.

In accordance with the December 20, 1995 letter from DDMAC, this submission hereby responds to the letter by providing complete responses to each of the comments. A copy of the December 20. 1995 letter immediately follows this letter to facilitate the Division's review of our submission.

Please note that the format of this submission identifies the Division's comment in bold print, and our response in unbolded print. The following revised launch materials are also included herein:

- Visual Aid (version A4847) - provided as both a highlighted copy (changes highlighted) and as a clean copy.
- Journal Ad (version A4895)
- Wholesaler Sell Sheet (version A4916-WSS)
- Pharmacy Sell Sheet (version A4916-RSS)
- Titration Guidelines Card (version A4898)
- Conversion Calculator (version A4894)

- File Card (version A4893)

If you have any questions or require additional information, please contact me at the number given below.

Sincerely yours,

Purdue Pharma L.P.
By:

Lee Ann Storey

Lee Ann Storey, RN, MPH
Assistant Director
Drug Regulatory Affairs and Compliance
The Purdue Frederick Company
(203) 854-7285

LAS/cby
Enclosures

Purdue Pharma L.P.

100 CONNECTICUT AVENUE, NORWALK, CONNECTICUT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

January 11, 1996

RESPONSE TO PROMOTIONAL QUESTIONS

TWO COPIES SUBMITTED UNDER SEPARATE COVER TO DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS

Robert Bedford, M.D.
Anesthetic/Critical Care & Abuse Drugs
Office of Drug Evaluation 3
Food and Drug Administration
HFD-1330, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 02857

RE: OXYCODONE HYDROCHLORIDE
NDA #20-553

Dear Dr. Bedford:

Reference is made to our New Drug Application, NDA #20-553 for OxyContin™ Controlled-Release Tablets, filed December 28, 1994 and approved December 21, 1995. Reference is also made to our promotional launch items filed October 12, 1995 and November 30, 1995; and to a December 20, 1995 letter received by us from the Division of Drug Marketing, Advertising and Promotion (DDMAC) which commented on the submitted launch items.

In accordance with the December 20, 1995 letter from DDMAC, this submission hereby responds to the letter by providing complete responses to each of the comments. A copy of the December 20. 1995 letter immediately follows this letter to facilitate the Division's review of our submission.

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If you have any questions or require additional information, please contact me at the number given below.

Sincerely yours,

Purdue Pharma L.P.
By:

Lee Ann Storey

Lee Ann Storey, RN, MPH
Assistant Director
Drug Regulatory Affairs and Compliance
The Purdue Frederick Company
(203) 854-7285

LAS/cby
Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

DEC 20 1995

TRANSMITTED VIA FACSIMILE

James H. Conover, Ph.D.
Executive Director
Drug Regulatory Affairs and Compliance
The Purdue Frederick Company
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

RE: NDA#20-553
OxyContin (Oxycodone hydrochloride)
MACMIS ID #3673

Dear Dr. Conover:

This is in response to The Purdue Frederick Company's (PF) October 12, 1995, and November 30, 1995, requests for comments on proposed launch materials for OxyContin. These materials include:

OxyContin Launch Visual Aid (version A4847)
OxyContin Journal Ad (version A4895)
OxyContin Wholesaler Sell Sheet (version A4916-WSS)
OxyContin Pharmacy Sell Sheet (version A4916-RSS)
OxyContin Titration Guidelines Card (version A4898)
OxyContin Conversion Calculator (version A4894)
OxyContin File Card (version A4893)

The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these materials and offers the comments that follow. Since many materials contain similar promotional concepts, DDMAC's comments on a specific claim or presentation should be applied to all similar claims or presentations throughout all current and future promotional materials.

Visual Aid A4847

- DDMAC suggests that the footnote information throughout this piece be enlarged because the font size is difficult to read and appears very light in some places.

Page 3

- **Prompt onset of relief - analgesic action within 1 hour in most patients**

  This statement would be misleading because onset of action

within one hour is not considered prompt relief. In fact, this is a much slower onset than the immediate release formulation, which has an onset of action within fifteen minutes. Additionally, analgesic action within an hour implies that full analgesia occurs within an hour, instead of analgesic onset of action within an hour. DDMAC suggests, for example, "Prompt onset of relief" be deleted and the remaining statement be revised to "analgesic onset within 1 hour in most patients."

- **Single-entity agent - contains no aspirin or acetaminophen which may be potentially toxic in high daily doses**

This statement would be misleading because "high daily doses" is ambiguous and overstates the toxicity. We suggest this be revised, for example, to "...which may be potentially toxic in maximal daily doses."

- **Common opioid side effects - often diminishing over time for many patients.**

DDMAC suggests "except for constipation" be added to this statement because this side effect does not diminish over time.

- **OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids is overdosage causing respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating and weakness.**

The balancing information should be enlarged because it is not presented with a prominence and readability reasonably comparable to the presentation of information about drug effectiveness.

Additionally, the sentence "The most serious risk associated with opioids is overdosage causing respiratory depression" would be misleading because it implies that respiratory depression only occurs with overdosage. DDMAC suggests this be revised, as consistent with the labeling, such as "The most serious risk associated with opioids, including OxyContin, is respiratory depression."

Page 4

- **The logical next step for patients no longer responding to or tolerating nonopioids: Add to or replace nonopioid with OxyContin.**

  Q 12 OxyContin - ideal for initial opioid therapy.

  OxyContin - The one to start with (Headline - all pages).

  These statements would be misleading because they imply that patients not responding to nonopioids should move directly to round-the-clock opiates as the next step in treatment. In fact, prn opioids for mild-to-moderate pain are usually added to the nonopioid therapy as the next step. OxyContin should not be presented as step 2 therapy (mild to moderate pain) on the analgesic pain ladder, because round-the-clock opioids are step 3 therapy (moderate to severe pain). Thus, DDMAC suggests these statements be revised such as "The logical next step for patients no longer responding to or tolerating nonopioids and prn opioids..., ideal for round-the-clock therapy, and the one to start with for round-the-clock therapy."

- **Patients are spared the added potential toxicities of high daily doses of ASA or APAP**

  See comment on under page three regarding maximal doses.

Page 5

- **Fewer 'peaks and valleys' than with immediate release oxycodone**

  This claims OxyContin provides a smoother plasma concentration but fails to include the oxycodone immediate release plasma concentration in the accompanying graph. If PF wishes to compare blood levels in the text, then DDMAC suggests that the blood levels for both dosage forms be presented in the graphic so that the reader can accurately interpret this claim.

- See previous comment on "The one to start with."

Page 6

- **Prompt onset of relief: Analgesic action within 1 hour in most patients.**

See previous comments.

- **Percent of patients experiencing onset of pain relief 90%.**

  This presentation would be misleading because, by referencing this one single-dose study in post-operative patients, it implies that OxyContin is indicated for this patient population. Thus, DDMAC recommends that if PF chooses to use this study to support the time to onset, that the introduction be qualified by prominently including the statement from the approved product labeling, "OxyContin is not recommended ... for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery).

  Additionally, this presentation alone would be misleading because it implies pain relief in 90% of patients. However, the studies for approval (402 A and 402 B) showed that 75% of chronic pain patients rated their pain control as good or excellent. Thus, we recommend this presentation also be revised to qualify that the 90% does not correlate to effective pain control.

- **Prompt pain relief plus a longer duration of action than Percocet, Vicodin, or Tylenol with Codeine**

  As discussed above, DDMAC would consider "prompt pain relief" to be misleading.

Page 7

- **Headline - The one to start with.**

  See previous comment.

- **Quality of Life Claims**

  DDMAC cannot comment on these claims until PF submits the following information as requested by telephone on December 1, 1995:
  1. survey validation,
  2. survey construction,
  3. statistical analysis of the results, and
  4. clinical study and methodology information

Page 8

- **Improved Contin delivery system allows both rapid and prolonged absorption**

  As discussed above concerning "prompt," DDMAC would consider "rapid" to be misleading and suggests the actual time be stated. For example, "initial release (within an hour)" would more accurately describe the delivery system.

- **Rapid Absorption/Prolonged Absorption**

  See previous comments regarding "prompt" or "rapid." Additionally, the delivery system does not change the absorption, it changes the way the drug is released. Therefore, DDMAC suggests that "rapid absorption" be revised to "initial release within an hour" and prolonged absorption to "prolonged release" or "prolonged delivery" to more accurately describe the biphasic delivery system.

  See previous comments regarding "pain relief begins promptly," and "...Oxycodone is rapidly released and absorbed quickly."

Page 9

- DDMAC suggests that PF include balancing information about the risk of overdose if the tablets are broken with the delivery system presentation.

Page 12

- **Steady state blood levels achieved in 24 hours.**

  This should be revised to "steady state blood levels achieved in 24 to 36 hours," as consistent with the approved labeling.

Page 14

- **Most side effects diminished over time, even as daily doses increased.**

  DDMAC suggests that this presentation include a statement that the most serious risk associated with opioids is respiratory depression.

Page 16 and 17

These pages present dosing and titration information but fail to include information from the warnings section of the approved labeling about high risk persons who may need a decrease in dosage. DDMAC suggests information be added to this presentation such as "respiratory depression is the most serious unintended effect of all opioid agonist preparations. Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. See Warnings and precautions."

Back Page

- **Small, color-coded tablets are easy to identify and swallow - an important benefit for patients on multiple medications**

  DDMAC questions whether the color-coded tablets are easy to identify for patients who are taking multiple medications that include other small, white, pink or yellow tablets.

  This summary page contains several statements which DDMAC has commented on in this letter. The back page should be consistent with the revisions made throughout the visual aid.

Journal Ad

Comments on the claims in the visual aid should be applied to the journal ad.

Wholesaler Sheet

- **Warning-May be habit forming**

  DDMAC suggests this statement be enlarged to increase its prominence because the typesize is difficult to read.

- **Strong demand expected**

  DDMAC has received the materials from the intent to prescribe survey. However, we cannot evaluate the data unless more information is provided about the methodology. Such a description should include how participants were selected, the refusal rate, the geographic distribution and other demographic data, and how the questionnaire was administered. For example, was it presented by the sales representative immediately after a presentation or was it

done in groups?

- **Balance information (back page).**

  See DDMAC's comments on the visual aid.

Pharmacy Sell Sheet

See comments on wholesaler sheet.

Titration Guidelines Card, Conversion Calculator, and File Card

See DDMAC's comments under visual aid.

If Purdue Frederick has any questions or comments, please contact the undersigned by facsimile (301) 594-6771 or by written communication at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, 5600 Fishers Lane, HFD-40, Room 17B-20, Rockville, MD 20857.

In all future correspondence regarding this matter, please refer to MACMIS ID #3673, in addition to the NDA number.

Sincerely,

Diane Shnitzler

Diane Shnitzler
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

RESPONSE TO COMMENTS

Visual Aid A4847

- **DDMAC suggests that the footnote information throughout this piece be enlarged because the font size is difficult to read and appears very light in some places.**

Reply:

The footnote information throughout the piece has been enlarged.

Page 3

- ***prompt onset of relief - analgesic action within 1 hour in most patients***

  This statement would be misleading because onset of action within one hour is not considered prompt relief. In fact, this is a much slower onset than the immediate release formulation, which has an onset of action within fifteen minutes. Additionally, analgesic action within an hour implies that full analgesia occurs within an hour, instead of analgesic onset of action within an hour. DDMAC suggests, for example, "Prompt onset of relief" be deleted and the remaining statement be revised to "analgesic onset within 1 hour in most patients."

Reply:

The statement

"**Prompt onset of relief -** analgesic action within 1 hour in most patients"

was revised to read,

"**Analgesic onset within 1 hour -** in most patients"

The above question states that the immediate-release formulation has an onset of action within fifteen minutes. Our data for the immediate-release formulation of oxycodone shows the onset of action is within 41 minutes. Please refer us to the studies which demonstrate a fifteen minute onset with immediate-release oxycodone, as we have not been able to find this in the literature.

- ***Single-entity agent - contains no aspirin or acetaminophen which may be potentially toxic in high daily doses***

  This statement would be misleading because "high daily doses" is ambiguous and overstates the toxicity. We suggest this be revised, for example, to "...which may be potentially toxic in maximal daily doses."

Reply:

The statement,

"**Single-entity agent -** contains no aspirin or acetaminophen which may be potentially toxic in high daily doses"

was revised to read,

"**Single-entity agent -** contains no aspirin or acetaminophen which may be potentially toxic in maximal daily doses"

- ***Common opioid side effects - often diminishing over time for many patients.***

  DDMAC suggests "except for constipation" be added to this statement because this side effect does not diminish over time.

Reply:

The statement,

"**Common opioid side effects -** often diminshing over time for many patients."

was revised to read,

"**Common opioid side effects** - often diminishing over time for many patients, except for constipation."

- ***OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose***

of oxycodone. The most serious risk associated with opioids is overdosage causing respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating and weakness.

The balancing information should be enlarged because it is not presented with a prominence and readability reasonably comparable to the presentation of information about drug effectiveness.

Additionally, the sentence "The most serious risk associated with opioids is overdosage causing respiratory depression" would be misleading because it implies that respiratory depression only occurs with overdosage. DDMAC suggests this be revised, as consistent with the labeling, such as "The most serious risk associated with opioids, including OxyContin, is respiratory depression."

Reply:

Visual aid revised accordingly

Page 4

- ***a) The logical next step for patients no longer responding to or tolerating nonopioids: Add to or replace nonopioid with OxyContin.***

  b) Q 12 OxyContin - ideal for initial opioid therapy.

  c) OxyContin - The one to start with (Headline - all pages).

  These statements would be misleading because they imply that patients not responding to nonopioids should move directly to round-the-clock opiates as the next step in treatment. In fact, prn opioids for mild-to-moderate pain are usually added to the nonopioid therapy as the next step. OxyContin should not be presented as step 2 therapy (mild to moderate pain) on the analgesic pain ladder, because round-the-clock opioids are step 3 therapy (moderate to severe pain). Thus, DDMAC suggests these statements be revised such as "The logical next step for patients no longer responding to or tolerating nonopioids and prn opioids..., ideal for round-the-clock therapy, and the one to start with for round-the-clock therapy."

Reply:

a) The statement,

"The logical next step for patients no longer responding to or tolerating nonopioids"

was replaced with,

"The logical next step for patients with persistent pain, no longer responding to or tolerating nonopioids"

The revision differs slightly from the suggested revision (**"The logical next step for patients no longer responding to or tolerating nonopioids and prn opioids..."),** because we disagree with the FDA interpretation of the WHO analgesic ladder[1]. Step 2 does not address dosing analgesics on a prn basis. Step 2 relates to adding an opioid to the therapeutic regimen in patients who have persisting pain in the presence of a non-opioid analgesic ± an analgesic adjuvant. While we recognize that common medical practice is to treat with non-opioids, then add or change to prn opioids or opioid/non-opioid combination products, and then advance to around-the-clock (a-t-c), this approach is not the best medical practice. This approach can lead to underdosing and episodes of breakthrough pain. Various publications and consensus statements support the use of a-t-c, not prn, medications for persistent pain syndromes. For example,

> "Administer analgesics regularly (not prn) if pain is present most of the day"[2]
>
> "Medications for persistent cancer-related pain should be administered on an around-the-clock basis with additional "as-needed" doses, because regularly scheduled dosing maintains a constant level of drug in the body and helps to prevent a recurrence of pain."[3]
>
> "Medication should be administered on a regular basis with the interval between doses based on the duration of the analgesic effect."[4]

While we recognize common medical practice, our goal, as a responsible company, is to foster education in the proper use of analgesics. In this way patients will be more likely to have continuing adequate pain control and relief.

[1] Cancer Pain Relief. World Health Organization. Geneva. 1986. p. 19
[2] Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. American Pain Society. 3rd edition 1992. p. 16
[3] Management of Cancer Pain. AHCPR Clinical Practice Guideline Number 9, March 1994, p. 39.
[4] Foley KM. The Treatment of Cancer Pain. New Eng J Med 313 (2): 84-95, 1985

b) The statement,

"Q 12 OxyContin - ideal for initial opioid therapy"

was revised to read,

"Q 12 OxyContin - ideal for initial around-the-clock (A-T-C) opioid therapy"

c) The statement,

"OxyContin - The one to start with (Headline - all pages)"

was revised to read,

"OxyContin - The one to start with (A-T-C)*

footnote and prior caption defines "A-T-C" as around the clock

- ***Patients are spared the added potential toxicities of high daily doses of ASA or APAP***

See comment on under page three regarding maximal doses.

Reply:

The statement,

"Patients are spared the added potential toxicities of high daily doses of ASA or APAP"

was revised to read,

"Patients are spared the added potential toxicities of maximal daily doses of ASA or APAP"

Page 5

- ***Fewer 'peaks and valleys' than with immediate release oxycodone***

  This claims OxyContin provides a smoother plasma concentration but fails to include the oxycodone immediate release plasma concentration in the accompanying graph. If PF wishes to compare blood levels in the text, then DDMAC suggests that the blood levels for both dosage forms be presented in the graphic so that the reader can accurately interpret this claim.

Reply:

The comparative statement, "Fewer peaks and valleys' than with immediate-release oxycodone" was deleted.

- ***See previous comment on "The one to start with."***

The statement,

"OxyContin - The one to start with (Headline - all pages)"

was revised to read,

"OxyContin - The one to start with (A-T-C)*

footnote and prior caption defines "A-T-C" as around the clock

Page 6

- ***Prompt onset of relief: Analgesic action within 1 hour in most patients.***

See previous comments.

Reply:

The statement, "Prompt onset of relief" was deleted.

The statement,

"Analgesic action within 1 hour in most patients"

was revised to read,

"Analgesic onset within 1 hour in most patients"

- ***Percent of patients experiencing onset of pain relief 90%.***

  This presentation would be misleading because, by referencing this one single-dose study in post-operative patients, it implies that OxyContin is indicated for this patient population. Thus, DDMAC recommends that if PF chooses to use this study to support the time to onset, that the introduction be qualified by prominently including the statement from the approved product labeling, "OxyContin is not recommended... for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery).

  Additionally, this presentation alone would be misleading because it implies pain relief in 90% of patients. However, the studies for approval (402A and 402B) showed that 75% of chronic pain patients rated their pain control as good or excellent. Thus, we recommend this presentation also be revised to qualify that the 90% does not correlate to effective pain control.

Reply:

Reference to postoperative patients was deleted from the footnote (i.e., "From a single-dose study in postoperative patients" was revised to, "From a single-dose study"). Because this reference to postoperative patients was deleted we do not believe it is necessary to include the suggested statement ["OxyContin is not recommended... for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery")]

The statement relating to 90% pertains to analgesic "onset", not pain relief. We have revised the statement to further clarify this (i.e., "Percent of patients experiencing onset of pain relief" was revised to, "Percent of patients experiencing analgesic onset")

- ***Prompt pain relief plus a longer duration of action than Percocet, Vicodin, or Tylenol with Codeine***

As discussed above, DDMAC would consider "prompt pain relief" to be misleading.

Reply:

The statement,

"Prompt pain relief plus a longer duration of action than Percocet, Vicodin, or Tylenol with Codeine"

was revised to read,

"Analgesic onset within one hour plus a longer duration of action than Percocet, Vicodin, or Tylenol with Codeine"

Page 7

- ***Headline - The one to start with.***

See previous comment.

Reply:

The statement,

"OxyContin - The one to start with (Headline - all pages)"

was revised to read,

"OxyContin - The one to start with (A-T-C)*

footnote and prior caption defines "A-T-C" as around the clock

- ***Quality of Life Claims***

DDMAC cannot comment on claims until PF submits the following information as requested by telephone on December 1, 1995:

1. **survey validation,**
2. **survey construction,**
3. **statistical analysis of the results, and**
4. **clinical study and methodology information**

Reply:

The above information was submitted to DDMAC on December 19, 1995.

The statement (as proposed prior to finalization of the Package Insert),

"Patients reported that OxyContin did not impair their ability to;
- Sleep
- Perform Normal Work
- Get along with other people
- Walk
- Enjoy Life

was revised, in accordance with the approved Package Insert, Section: CIINICAL TRIALS, Subsection: Studies in Non-Cancer Pain, to

"- In this study, OxyContin 20 mg q12h...
- Significantly decreased pain
- Improved quality of life, mood and sleep"

We believe the Package Insert most accurately describes the results of this study.

Page 8

- ***Improved Contin delivery system allows both rapid and prolonged absorption***

As discussed above concerning "prompt," DDMAC would consider "rapid" to be misleading and suggests the actual time be stated. For example, "initial release (within an hour)" would more accurately describe the delivery system.

Reply:

The statement,

"Improved Contin® delivery system allows both rapid and prolonged absorption."

was revised to read,

"Improved Contin® delivery system allows both rapid and prolonged release."

- ***Rapid absorption/Prolonged Absorption***

See previous comments regarding "prompt" or "rapid." Additionally, the delivery system does not change the absorption, it changes the way the drug is released. Therefore, DDMAC suggests that "rapid absorption" be revised to "initial release within an hour" and prolonged absorption to "prolonged release" or "prolonged delivery" to more accurately describe the biphasic delivery system.

See previous comments regarding "pain relief begins promptly," and "...Oxycodone is rapidly released and absorbed quickly."

Reply:

a) The statement,

Rapid absorption Pain relief begins promptly as a portion of the active oxycodone is rapidly released and absorbed quickly."

was revised to read,

Rapid release Analgesic onset within one hour as a portion of the active oxycodone is released and absorbed."

b) The statement,

"Prolonged absorption"

was revised to read,

"Prolonged release"

In addition, the layout of the illustration text was changed so as not to give the inadvertent impression that the rapid release occurs only in the stomach, and prolonged release occurs only in the intestine. Release of drug is not dependent upon its location in the gastrointestinal tract (i.e., no pH dependence).

To further define the tablet release characteristics, the statement "pH independence" assures...Minimal effect of stomach contents on absorption-bioavailability unaffected by food" was moved from the bottom of page 9 to the bottom of page 8.

Page 9

- **DDMAC suggests that PF include balancing information about the risk of overdose if the tablets are broken with the delivery system presentation.**

Reply:

This balancing information was added to the bottom of page 9.

Page 12

- ***Steady state blood levels achieved in 24 hours.***

This should be revised to "steady state blood levels achieved in 24 to 36 hours," as consistent with the approved labeling.

Reply:

The statement,

"Steady state blood levels achieved in 24 hours"

was revised to read,

"Steady -State blood levels achieved in 24-36 hours

Page 14

- ***Most side effects diminished over time, even as daily doses increased.***

DDMAC suggests that this presentation include a statement that the most serious risk associated with opioids is respiratory depression.

Reply:

a) The statement,

"Common opioid side effects; many diminish over time."

was revised to read,

"Common opioid side effects; many diminish over time except for constipation."

b) the following statement was added as a bullet point under the side effect Table,

"- The most serious risk associated with opioids is respiratory depression."

c) The statement,

"-Most side effects diminished over time, even as daily doses increased"

was revised to read,

"Most side effects diminished over time, except for constipation, even as daily doses increased"

Page 16 and 17

These pages present dosing and titration information but fail to include information from the warnings section of the approved labeling about high risk persons who may need a decrease in dosage. DDMAC suggests information be added to this presentation such as "respiratory depression is the most serious unintended effect of all opioid agonist preparations. Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant

patients, or when opioids are given in conjunction with other agents that depress respiration. See Warnings and Precautions."

Reply:

The following statement was added,

"Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. See WARNINGS and PRECAUTIONS."

The proposed initial sentence, "respiratory depression is the most serious unintended effect of all opioid agonist preparations." was not added because we believe respiratory depression is addressed sufficiently in the remainder of the statement as well as on pages 3 and 14 of this visual aid.

Back Page

- ***Small, color-coded tablets are easy to identify and swallow - an important benefit for patients on multiple medications***

DDMAC questions whether the color-coded tablets are easy to identify for patients who are taking multiple medications that include other small, white, pink or yellow tablets.

Reply:

The statement,

"-Small, color-coded tablets are easy to identify and swallow- an important benefit for patients on multiple medications"

was revised to read,

"- Small, color-coded tablets are easy to identify and swallow"

This summary page contains several statements which DDMAC has commented on in this letter. The back page should be consistent with the revisions made throughout the visual aid.

Reply:

The back page has been revised to be consistent with the revisions made throughout the visual aid.

In addition to the above changes, pages 16 and 17 were revised to delete the statements pertaining to "q3-4h prn" and to add the statement " See professional prescribing information for immediate-release oxycodone."*

Throughout the visual aid the statement, "Please see accompanying full prescribing information." was revised to read, "Please see accompanying professional prescribing information."

Journal Ad

Comments on the claims in the visual aid should be applied to the journal ad.

Reply:

Revised in accordance with the visual aid.

Wholesaler Sheet

- ***Warning-May be habit forming***

  DDMAC suggests this statement be enlarged to increase its prominence because the type size is difficult to read.

Reply:

Revised in accordance with the visual aid.

- ***Strong demand expected***

  DDMAC has received the materials from the intent to prescribe survey. However, we cannot evaluate the data unless more information is provided about the methodology. Such a description should include how participants were selected, the refusal rate, the geographic distribution and other

demographic data, and how the questionnaire was administered. For example, was it presented by the sales representative immediately after a presentation or was it done in groups?

- ***Balance information (back page).***

See DDMAC's comments on the visual aid.

Reply:

In order to expedite distribution of the Wholesaler sheet, we deleted all promotional statements from this sheet. Therefore statements based on the intent to prescribe survey were also deleted.

Attached is a copy of the redesigned Wholesaler Sheet.

Pharmacy Sell Sheet

See Comments on wholesaler sheet.

Reply:

In order to expedite distribution of the Pharmacy Sell sheet, we deleted any promotional statements from this sheet.

Attached is a copy of the redesigned Pharmacy Sell Sheet.

Titration Guidelines Card, Conversion Calculator, and File Card

See DDMAC's comments under visual aid.

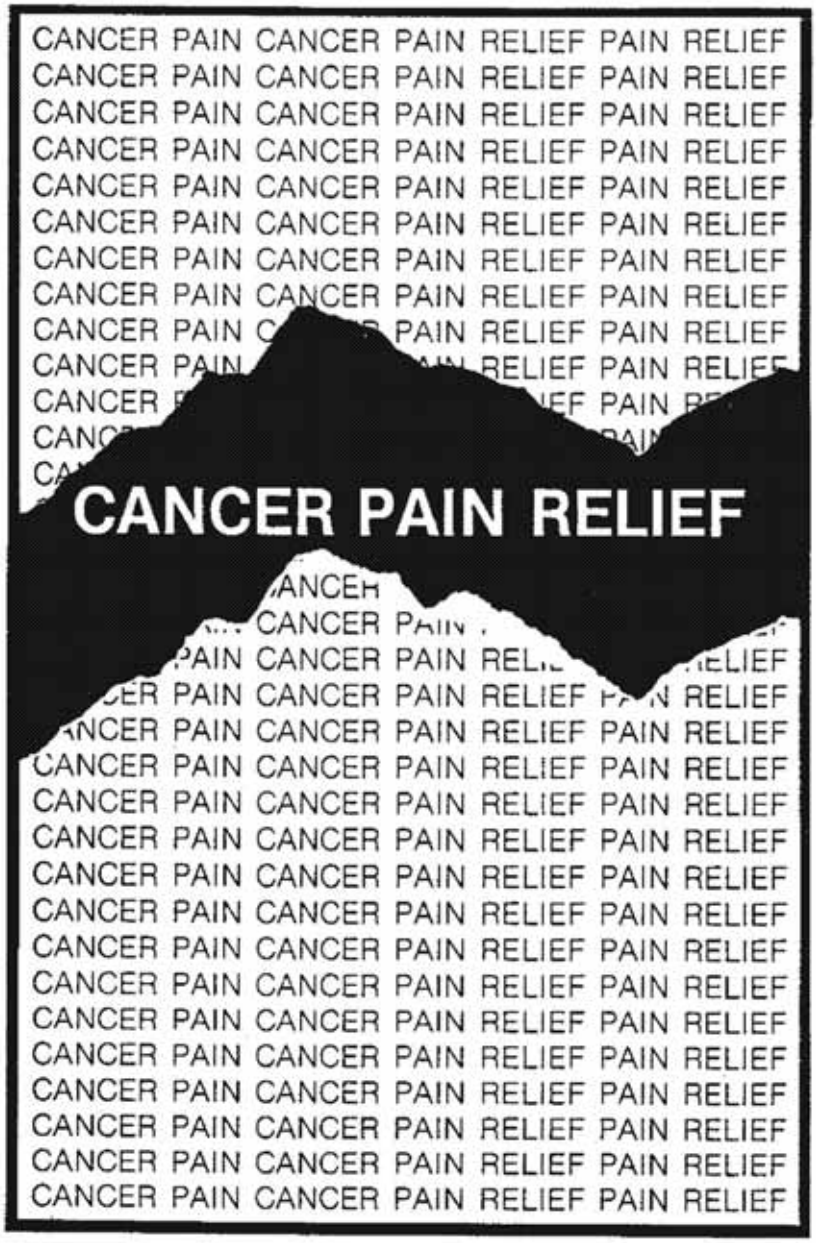
Reply:

Revised in accordance with the visual aid.

The Conversion Calculator (refer to highlighted version) has been revised to:

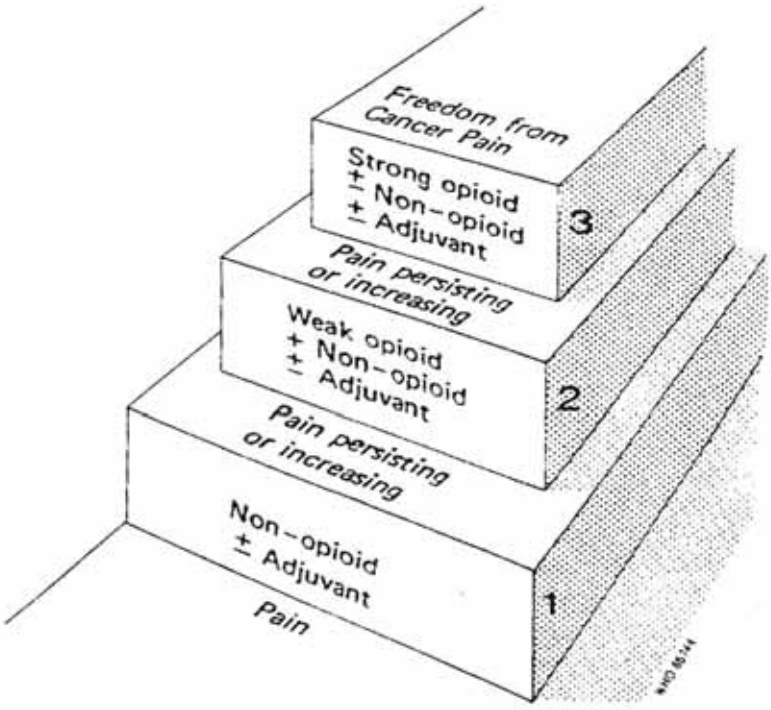
1) round down the recommended conversion doses to allow for use of one tablet strength. This cautionary change was made to prevent possible administration errors if patients should be directed to take two tablet strengths as the prescribed dose. The conversion doses remain consistent with Table 4 in the DOSAGE AND ADMINISTRATION Section of the Package Insert.

2) alter the recommended conversion dose of OxyContin tablets when patients are converted from controlled-release oral morphine(MS Contin®). These doses were altered to better coordinate with MS Contin® dosage strengths.



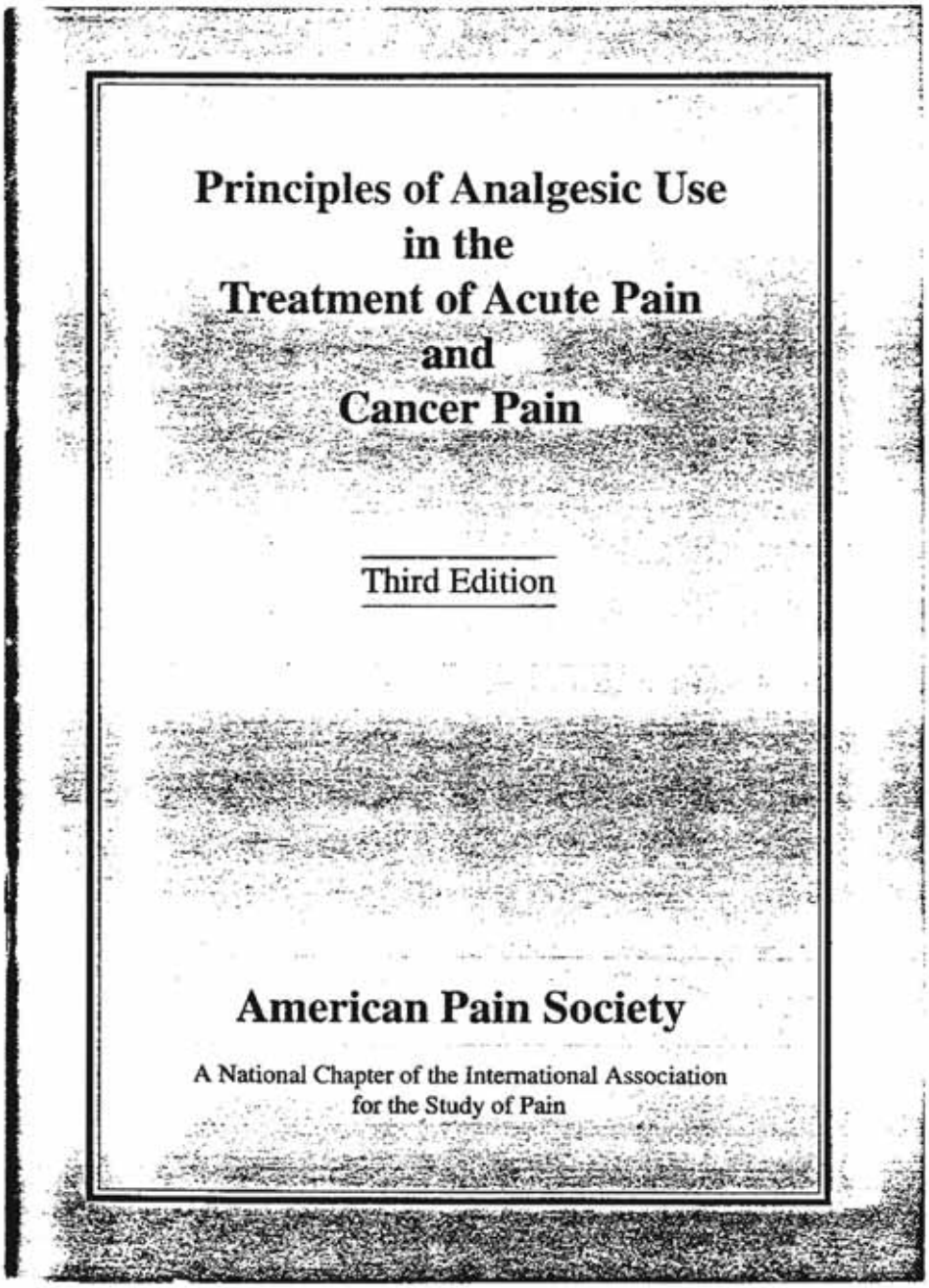
CANCER PAIN RELIEF

World Health Organization, Geneva



Adjuvant drugs are often needed in patients with pain secondary to nerve injury. There is evidence to suggest that they provide additive analgesic effects (*49*) and controlled studies demonstrate the analgesic efficacy of, for example, amitriptyline (*16*). Corticosteroids are commonly used in patients with cancer both as chemotherapeutic agents and as analgesics. Several studies have reported relief of pain by corticosteroids in patients with epidural spinal cord compression or infiltration of a nerve by the tumour, and also in metastatic bone disease (*50, 51*). Useful adjuvant drugs are listed in Annex 1, Table 3.

On the basis of considerable clinical experience and of controlled studies of analgesics, a series of important principles have been established:


Principles of Analgesic Use
in the
Treatment of Acute Pain
and
Cancer Pain
Third Edition
American Pain Society
A National Chapter of the International Association
for the Study of Pain

venous patient-controlled analgesia following cesarean section, mean demand rates varied from 0.6 to 5.2 mg per hour. This great variability underscores the need to write analgesic orders that include provision for supplementary doses, and to use intravenous boluses and infusions to provide rapid relief of severe pain. Elderly patients and patients with central nervous system disease should be observed with particular care during dose titration to minimize adverse reactions. Intramuscular morphine produces a longer duration of analgesia in older patients, in part related to prolonged elimination from plasma (Kaiko et al., 1986). For patients over 70, one should consider lowering the starting doses in Table 3 by 25% to 50%.

c. Give each analgesic an adequate trial by dose titration (i.e., increasing the dose up to the appearance of limiting side effects) before switching to another drug.

2. Administer analgesics regularly (not prn) if pain is present most of the day.

This should be done after establishing the optimal dose by titration—that is, giving a typical starting dose and increasing or decreasing the dose according to the degree of pain relief and side effects experienced by the patient. Once the optimal dose requirements for a 24-hour period have been established by titration, the analgesics can be administered on a scheduled, around-the-clock basis with fewer side effects. A prn order for a supplementary opioid dose between regular doses is an essential backup. If *only* prn medications are used, it may take several hours and higher doses of opioids to relieve pain, leading to a cycle of undermedication and pain alternating with periods of overmedication and drug toxicity. It is particularly important that children and patients with limited communication skills do not receive a prn-only regimen. If pain is present for only a few brief periods during the day, the patient can regularly be offered a standard analgesic dose, or the choice of a larger or smaller dose.

3. Become familiar with the dose and time-course of several strong opioids.

While morphine is the standard strong opioid, all morphine-like agonists (see Table 3, a) provide similar qualities of analgesia and similar qualities and frequency of side effects. In practice, however, individual

Clinical Practice Guideline

Number 9

Management of Cancer Pain

U.S. Department of Health and Human Services
Public Health Service
Agency for Health Care Policy and Research

Clinical Practice Guideline

Management of Cancer Pain

3 Pharmacologic Management

Recommendations

13. An essential principle in using medications to manage cancer pain is to individualize the regimen to the patient. (A)
14. The simplest dosage schedules and least invasive pain management modalities should be used first. (Panel Consensus)
15. Pharmacologic management of mild to moderate cancer pain should include an NSAID or acetaminophen. unless there is a contraindication. (A)
16. When pain persists or increases. an opioid should be added. (A)
17. Treatment of persistent or moderate to severe pain should be based on increasing the opioid potency or dose. (A)
18. Medications for persistent cancer-related pain should be administered on an around-the-clock basis with additional "as-needed" doses, because regularly scheduled dosing maintains a constant level of drug in the body and helps to prevent a recurrence of pain. (A)
19. Patients receiving opioid agonists should not be given a mixed agonist-antagonist because doing so may precipitate a withdrawal syndrome and increase pain. (B)
20. Meperidine should not be used if continued opioid use is anticipated. (B)
21. Opioid tolerance and physical dependence are expected with long-term opioid treatment and should not be confused with addiction. (Panel Consensus)
22. The oral route is the preferred route of analgesic administration because it is the most convenient and cost-effective method of administration. When patients cannot take medications orally, rectal and transdermal routes should be considered because they are also relatively noninvasive. (Panel Consensus)
23. Intramuscular administration of drugs should be avoided because this route can be painful and inconvenient, and absorption is not reliable. (B)
24. Failure of maximal systemic doses of opioids and coanalgesics should precede the consideration of intraspinal analgesic systems. (Panel Consensus)

13. Lane HC. Immunologic abnormalities. In: Fauci AS, ed. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. Ann Intern Med 1984; 100:98-9.
14. Murray HW, Rubin BY, Masur H, Roberts RB. Impaired production of lymphokines and immune (gamma) interferon in the acquired immunodeficiency syndrome. N Engl J Med 1984; 310:883-9.
15. Ciobanu N, Weite K, Kruger G, et al. Defective T-cell response to PHA and mitogenic monoclonal antibodies in male homosexuals with acquired immunodeficiency syndrome and its *in vivo* correction by interleukin 2. J Clin Immunol 1982; 3:332-40.
16. Lane HC, Masur H, Gelmann EP, et al. Correlation between immunologic function and clinical subpopulations of patients with the acquired immune deficiency syndrome. Am J Med 1985; 78:417-22.
17. Prince HE, Kermani-Arab V, Fahey JL. Depressed interleukin 2 receptor expression in acquired immune deficiency and lymphadenopathy syndromes. J Immunol 1984; 133:1313-7.
18. Benveniste E, Schruff R, Stevens RH, Gottlieb MS. Immunoregulatory T cells in men with a new acquired immunodeficiency syndrome. J Clin Immunol 1983; 3:359-67.
19. Update on acquired immune deficiency syndrome (AIDS) — United States. MMWR 1982; 31:507-14.
20. Lane HC, Whalen G, Fauci AS. Antigen-induced human T cell help: precursor frequency, radiation sensitivity, and allogeneic effects. J Clin Invest 1983; 72:636-47.
21. Pellegrino MA, Ferrone S, Dierich MP, Reisfield RA. Enhancement of sheep red blood cell human lymphocyte rosette formation by the sulfhydryl compound 2-aminoethylisothiouronium bromide. Clin Immunol Immunopathol 1975; 3:324-33.
22. Stewart WE. The interferon system. 2nd ed. New York: Springer-Verlag, 1981:13-26.
23. Depper JM, Leonard WJ, Waldmann TA, Greene WC. A monoclonal antibody which recognizes the human receptor for T cell growth factor: functional effects and use as a probe to investigate receptor regulation. In: Pick E, ed. Lymphokines. Vol. 9. New York: Academic Press, 1984:127-52.
24. Depper JM, Leonard WJ, Krönke M, Waldmann TA, Greene WC. Augmented T cell growth factor expression in HTLV-1-infected human leukemic T cells. J Immunol 1984; 133:1691-5.
25. Depper JM, Leonard WJ, Krönke M, et al. Regulation of interleukin-2 receptor expression: effects of phorbol diester, phospholipase-C, and reexposure to antigen or lectin. J Immunol (in press).
26. Reinherz EL, Kung PC, Goldstein G, Schlossman SF. Further characterization of the human inducer T cell subset defined by monoclonal antibody. J Immunol 1979; 123:2894-6.
27. Gupta S, Safai B. Deficient autologous mixed lymphocyte reaction in Kaposi's sarcoma associated with deficiency of Leu-3$^+$ responder T cells. J Clin Invest 1983; 71:296-300.
28. Smolen JS, Bettelheim P, Köller U, et al. Defect in intercellular communication in patients with hemophilia. Fed Proc 1984; 43:1922.
29. Hausman PB, Stites DP, Stobo JD. Antigen-reactive T cells can be activated by autologous macrophages in the absence of added antigen. J Exp Med 1981; 153:476-81.
30. Dalgleish AG, Beverley PCL, Clapham PR, Crawford DH, Greaves MF, Weiss RA. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature 1984; 312:763-7.
31. Klatzmann D, Champagne E, Chamaret S, et al. T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. Nature 1984; 312: 767-8.
32. Belsito DV, Sanchez MR, Baer RL, Valentine F, Thorbecke GJ. Reduced Langerhans' cell Ia antigen and ATPase activity in patients with the acquired immunodeficiency syndrome. N Engl J Med 1981; 310:1279-82.

MEDICAL PROGRESS

THE TREATMENT OF CANCER PAIN

KATHLEEN M. FOLEY, M.D.

ADVANCES in the diagnosis and treatment of cancer, coupled with an expanded understanding of the physiology, pharmacology, and psychology of pain perception, have led to improved care of the patient with pain from cancer.[1] Improved methods of cancer diagnosis and treatment provide the best approach to managing pain by treating its cause. Before the start of antitumor therapy or when such therapy is unsuccessful or irreversible injury to bone, soft tissue, or nerve has occurred, however, adequate pain control is essential.

Management of pain in patients with cancer requires specific expertise that includes a knowledge of the clinical pain syndromes that are common in cancer and their pathophysiologic mechanisms, the psychological state of the patient, and the indications and limitations of the available therapeutic approaches. Clinical experience suggests that patients with cancer pain are treated most effectively with a multidisciplinary approach that includes adequate analgesic drug therapy, neurosurgical and anesthetic procedures, behavioral methods, and supportive care.[2-5]

The goal of pain therapy for patients receiving active treatment is to provide them with sufficient relief to tolerate the diagnostic and therapeutic approaches required to treat the cancer. For patients with advanced disease, pain control should be sufficient to allow the patients to function at a level that they choose and to die relatively free of pain.[6,7] Critical to the management of cancer pain is the establishment of a trusting relationship between the patient and a physician who takes the pain seriously and assesses its nature and severity.

EPIDEMIOLOGY

Large-scale epidemiologic studies of the incidence and severity of cancer pain are lacking, but numerous studies in specialized medical care settings have demonstrated that the prevalence of pain increases with the progression of disease. Patients with cancer frequently have multiple causes of pain.[8] Some 15 per cent of patients with nonmetastatic cancer have pain.[9] One third of adults and children with metastatic cancer report pain that interferes with and reduces their activity level and requires the use of analgesics.[10] With advanced disease, 60 to 90 per cent of patients report

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Supported in part by grants from the U.S. Public Health Service (CA 32897 and DA 01707) and the Patricia Drake Hemingway Fund.

substantial pain.[3,11,12] It is postulated that 25 per cent of all patients with cancer throughout the world die without relief from severe pain.[2] To remedy this situation and as part of a broader cancer program, the Cancer Unit of the World Health Organization has formulated a pain-relief program to conduct an epidemiologic investigation of cancer pain throughout the world, to provide guidelines for pain management, particularly in patients with advanced disease, and to encourage national governments to help make therapeutic approaches available, specifically oral narcotic drug therapy.[13]

Types of Pain

Patients with cancer have two types of pain: acute and chronic. This division is based on an increased understanding of the mechanisms of pain transmission and the recognition that the central modulation of acute and chronic pain states may differ, along with their clinical management and response to treatment.[14,15] For this discussion the definition of pain proposed by the International Association for the Study of Pain is most useful: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[16] Because pain is a subjective experience, evaluation of it is difficult. The physician has limited objective signs to confirm the severity of reported pain. The patient and physician are best served if the physician believes the patient's report.

Acute pain is characterized by a well-defined temporal pattern of onset. It is generally associated with subjective and objective physical signs and hyperactivity of the autonomic nervous system. These signs serve as objective evidence to the physician, substantiating the patient's report of pain. In contrast, chronic pain is pain that persists longer than six months, in which adaptation of the autonomic nervous system occurs. Patients with chronic pain lack the objective signs common to acute pain. Chronic pain leads to marked changes in personality, life style, and functional ability. Such pain requires an approach that encompasses not only treatment of the cause of the pain but also treatment of its psychological and social consequences.[15,17]

Patients with chronic or acute pain from cancer can be further subdivided, providing the physician with a useful classification when considering therapeutic approaches (Table 1).

Group I comprises patients with acute cancer-related pain. A subgroup of this category includes patients in whom pain is the major symptom leading to the diagnosis of cancer. For this group, pain has a special meaning as the harbinger of their illness. The occurrence of pain during the course of the illness or after successful therapy has the immediate implication of recurrent disease. Determination of the cause of the pain may present a diagnostic problem, but effective treatment of the cause — e.g., irradiation of bone metastases — is usually possible and is associated with dramatic pain relief in the majority of patients.

Table 1. Types of Patients with Pain from Cancer.

I. Patients with acute cancer-related pain
a. Associated with the diagnosis of cancer
b. Associated with cancer therapy (surgery, chemotherapy, or radiation)
II. Patients with chronic cancer-related pain
a. Associated with cancer progression
b. Associated with cancer therapy (surgery, chemotherapy, or radiation)
III. Patients with preexisting chronic pain and cancer-related pain
IV. Patients with a history of drug addiction and cancer-related pain
a. Actively involved in illicit drug use
b. In methadone maintenance programs
c. With a history of drug abuse
V. Dying patients with cancer-related pain

The second subgroup includes patients who have acute pain associated with cancer therapy — e.g., pain after surgery or secondary to the acute effects of chemotherapy. The cause of the pain is readily identified, and its course is predictable and self-limited. Such patients endure pain for the promise of a successful outcome.

Group II, which consists of patients with chronic cancer-related pain, represents difficult diagnostic and therapeutic problems. This group can be subdivided into patients with chronic pain from tumor progression and those with chronic pain related to cancer treatment. Both subgroups have pain that has persisted for more than six months.

In patients with chronic pain associated with the progression of disease — e.g., those with carcinoma of the pancreas — the pain escalates in intensity, and combinations of antitumor therapy, analgesic drug therapy, anesthetic blocks, and behavioral approaches to pain control are all attempted with varying degrees of success.

Psychological factors play an important part in this group of patients, in whom palliative therapy may be of little value and is physically debilitating.[11,18] The sense of hopelessness and fear of impending death may add to and exaggerate the pain, which in turn contributes to the overall suffering of the patient. Identification of both the pain and the suffering component is essential to the provision of adequate therapy. Saunders has used the phrase "total pain" to describe the etiologic components other than the noxious physical stimulus, including emotional, social, bureaucratic, financial, and spiritual pain.[4] Those caring for this group of patients must be concerned with all aspects of distress and discomfort if the experience of physical pain is to be alleviated. The chronicity of the pain is associated with a series of psychological signs — e.g., disturbances in sleep, reduction in appetite, impaired concentration, and irritability — and with clinical signs and symptoms mimicking a depressive disorder.[15]

Patients with chronic pain associated with cancer therapy usually require treatment directed at the symptoms, not the cause. Treatment of the pain is

often limited by the lack of available methods to remove the cause of the pain — e.g., a traumatic neuroma. This group of patients closely parallels those in the general population with chronic, intractable pain. Identification of this group of patients is imperative, because recognition of the cause of the pain as independent of the cancer markedly alters the patient's therapy, prognosis, and psychological state. All approaches intended to maintain the functional status of the patient should be employed.[15,17] Approaches other than drug therapy provide effective alternatives for pain management. This group is increasing in size and accounts for 25 per cent of patients referred to one cancer pain clinic.[10]

Group III includes patients with a history of chronic, nonmalignant pain who have cancer and associated pain. Psychological factors play an important part in these patients, whose psychological and functional status is already compromised. They are at high risk of further functional incapacity and escalating chronic pain. However, their history should not be used in a punitive way to minimize their complaints. Identification of this group of patients as a high-risk group helps to improve their psychological assessment and intervention.

Group IV includes patients with a history of drug addiction who have cancer-related pain. Three subgroups can be identified: patients actively involved in illicit drug use and drug-seeking behavior, those receiving methadone in a maintenance program, and those who have not used drugs for several years. Undertreatment with analgesic drugs occurs most commonly in this group of patients. Assessment of reported pain by physicians and nurses is colored by the fact that the pain symptoms are confused with drug-seeking behavior. Attention to the medical and psychological needs of these patients requires individualized assessment and consultation with experts in drug-related problems.[18] The first subgroup represents a major management problem, straining the most tolerant of medical care systems. Pain in the other two subgroups is readily managed, with the recognition that the psychological stresses consequent to the pain and cancer may place the patient at high risk for recidivism.

Group V includes dying patients with pain. In this group diagnostic and therapeutic considerations should be directed at maintaining the comfort of the patient. The issues of hopelessness, death, and dying become prominent, and the suffering component of the illness must be addressed. Inadequate control of pain exacerbates the suffering and demoralizes both the family and the medical personnel, who feel that they have failed in treating the patient's pain at a time when adequate treatment may matter most. Rapid escalation of analgesic drug therapy and attempts to ameliorate the psychological symptoms should be employed. The risk–benefit ratios associated with analgesic approaches become less of an issue when the goal of pain therapy is the comfort of the patient.

These types of cancer pain point up the necessity of understanding the psychological needs of the patient and the temporal factors in order to assess the pain and manage it appropriately.

Cancer pain has also been classified according to a series of common pain syndromes and their pathophysiologic mechanisms.[12] The pain syndromes that commonly occur in patients with cancer have been divided into three major categories.

The first and most common cause of pain in patients with cancer is that associated with direct tumor involvement. This accounted for 78 per cent of pain problems in a survey of the Memorial Sloan–Kettering Cancer Center inpatient population[5] and for 62 per cent of problems in an outpatient survey.[9] Metastatic bone disease, nerve compression or infiltration, and hollow viscus involvement are the most common causes of pain from direct tumor involvement.

The second group of pain syndromes are those associated with cancer therapy. This group accounts for approximately 19 per cent of pain problems in an inpatient population and 25 per cent of problems in outpatients. It includes pain that occurs in the course of or as a result of surgery, chemotherapy, or radiation therapy.

The third category of pain syndromes includes those unrelated to the cancer or the cancer therapy. Approximately 3 per cent of inpatients have pain unrelated to cancer or cancer therapy, and this figure increases to 10 per cent when an outpatient population is surveyed.

The pathophysiologic mechanisms of these common pain syndromes are not well understood. It is currently thought that a series of neuropharmacologic and neurophysiologic changes occur in bone, soft tissue, lymphatics, blood vessels, nerve and viscera, activating and sensitizing nociceptors and mechanoreceptors by mechanical (tumor compression or infiltration) or chemical (metastases in bone) stimuli. Acute, intermittent, or continuous pain results. Most therapeutic approaches are partially effective in controlling this kind of pain.[19] In contrast, pain from nerve injury after nerve section or chronic tumor infiltration or compression produces partial damage of axons and nerve membranes, which become extremely sensitive to any mechanical or chemical stimuli. Chronic unremitting pain results, which is poorly controlled by the majority of therapeutic approaches. Experimental studies indicate that pain from deafferentation leads to central neuronal hyperactivity in the spinal cord and, possibly, in the thalamus.[20]

These different physiologic mechanisms account in part for the differences in the responses of various types of cancer pain to analgesic, neurosurgical, and anesthetic approaches. For example, drug therapy and neurosurgical procedures are often effective in managing pain from lumbosacral plexopathy in its early acute stage, but once deafferentation has occurred, the success of such procedures diminishes rapidly.[20]

Management of Cancer Pain

There are certain general principles that should be followed in evaluating all patients with cancer and pain.[21] Lack of attention to these principles is the major cause of misdiagnosis and inappropriate management of a specific pain syndrome. The principles include a complete assessment of the history of pain and an evaluation of the psychosocial status of the patient. A careful medical and neurologic examination must be coupled with the use of appropriate diagnostic procedures to determine the nature of the pain. Early treatment with analgesics markedly improves the patient's ability to participate in these procedures. No patient should be inadequately evaluated because of pain. Continual reassessment of the patient's response to prescribed therapy provides the best method of validating the accuracy of the initial diagnosis. If the response to therapy is less than predicted or if exacerbation of pain occurs, reassessment of the treatment approach or a search for a new cause of pain should be considered. Management of pain in patients with cancer requires continuity of care from the diagnosis to treatment.[22]

Therapeutic Approaches

Non-narcotic, narcotic, and adjuvant analgesic drugs are the mainstay of therapy for patients with cancer pain. Effective use of these drugs requires an understanding of their clinicopharmacologic characteristics, with selection of a particular drug and dose geared to the needs of the individual patient. Neurosurgical, anesthetic, and behavioral approaches are commonly used in combination with drug therapy.

Changing attitudes toward the use of narcotic analgesics for cancer pain coupled with the recognition of the dynamic complexity of pain modulation have led to reassessment of the role of anesthetic and neurosurgical approaches. These approaches are most useful for managing localized pain before the development of serious nerve injury and a consequent deafferentation state. Although these procedures have been widely used, controlled studies of their effectiveness, as compared with that of other methods of pain control, are lacking. Published reports provide survey data on techniques and successful outcome in small numbers of patients.

These techniques require specific expertise, and certain guidelines apply to their use. These include a thorough evaluation of the nature of the pain and the patient's prognosis, an adequate prior trial of analgesic drug therapy and anticancer therapy, and the patient's awareness of the potential risks and benefits of the planned procedures. The types of anesthetic and neurosurgical procedures are listed in Tables 2 and 3. Historically, these procedures have been employed late in the course of a patient's illness, and full assessment of their efficacy has been limited by disease progression and diffuse as well as focal pain. Many patients prefer to defer these procedures until they complete their anticancer therapy, with the hope that such therapy will provide relief. Also, when informed about the small but potential risk of neurologic impairment associated with these procedures, many patients are not willing to accept such a risk for pain control alone.

There is a need to develop strategies for the appropriate use of these procedures. A detailed review of them is beyond the scope of this discussion. Drug therapy is stressed in the following discussion, because all physicians caring for patients with pain must develop competence and confidence in the use of drugs.

Drug Therapy

Non-narcotic Agents

Non-narcotic analgesics are the first-line agents for the management of mild to moderate cancer pain.[22-25] In patients with severe pain these drugs serve to potentiate the effects of narcotic analgesics. Non-narcotic analgesics have a ceiling effect, and their long-term use is limited by gastrointestinal and hematologic side effects. In contrast to narcotic analgesics, non-narcotic agents do not cause tolerance or physical dependence.

There is increasing evidence to suggest that these drugs may have a unique role in the management of certain kinds of pain from bone metastases.[26-28] Anecdotal reports indicate that both aspirin and indomethacin relieve bone pain, and in an animal tumor model, aspirin has been shown to have antitumor effects. These effects are thought to be mediated in part through inhibition of prostaglandin synthesis, specifically prostaglandin E_2, which is important in the development of bone metastases in solid tumors.

Table 2. Neuroablative, Neurostimulatory, and Neuropharmacologic Procedures for Relief of Pain from Cancer.

Site	Procedure		
	Neuroablative	Neurostimulatory	Pharmacologic
Peripheral nerve	Neurectomy	Transcutaneous and percutaneous electrical nerve stimulation	Local anesthetics
Nerve root	Rhizotomy		Local anesthetics Neurolytic agents
Spinal cord	Dorsal-root entry-zone lesions Cordotomy Myelotomy	Dorsal-column stimulation	Epidural and intrathecal local anesthetics and opiates
Brain stem	Mesencephalic tractotomy	Periaqueductal stimulation	Intraventricular opiates
Thalamus	Thalamotomy	Thalamic stimulation	
Cortex	Cingulumotomy Frontal lobotomy		
Pituitary	Transsphenoidal hypophysectomy		Chemical hypophysectomy

Table 3. Types of Anesthetic Procedures Commonly Used for Cancer Pain.

Type of Procedure	Most Common Indications
Nerve block	
Peripheral	Pain in discrete dermatomes in chest and abdomen
Epidural	Unilateral lumbar or sacral pain
	Midline perineal pain
	Bilateral lumbosacral pain
Intrathecal	Midline perineal pain
	Bilateral lumbosacral pain
Autonomic	
Stellate ganglion	Reflex sympathetic dystrophy (e.g., frozen shoulder)
	Arm pain
Lumbar sympathetic	Reflex sympathetic dystrophy
	Lumbosacral plexopathy
	Vascular insufficiency of the lower extremity
Celiac plexus	Midabdominal pain
Continuous epidural infusion with local anesthetics	Unilateral and bilateral lumbosacral pain
	Midline perineal pain
Chemical hypophysectomy	Diffuse bone pain
Inhalation therapy	Generalized pain
	Incident pain
Trigger-point injection	Focal muscle pain

The choice and use of these drugs must be individualized, with the patient receiving maximal levels of one drug before another is tried. Combinations of nonsteroidal and antiinflammatory drugs that produce additive analgesia remain controversial. If pain control is ineffective or the non-narcotic agents are poorly tolerated, the use of narcotic analgesics is indicated.

Narcotic Analgesics

The narcotic analgesics are classified as agonist or antagonist drugs, depending on their ability to bind to opiate receptors and produce analgesia. The narcotic agonist drugs, such as morphine, bind to specific opiate receptors, resulting in analgesia. These drugs are commonly used in the management of cancer pain. The narcotic antagonist drugs block the effect of morphine at its receptor. Included in this category is a group of drugs with analgesic properties referred to as "mixed agonist–antagonist" drugs.[29] These drugs are of limited use in patients with cancer for several reasons: they produce psychotomimetic effects with increasing doses; except for pentazocine, they are available only for parenteral administration (nalbuphine and butorphanol); oral pentazocine is available only in combination with naloxone, aspirin, or acetaminophen; and they precipitate withdrawal in narcotic-dependent patients. One of the newer drugs in this class, buprenorphine, has been shown to be clinically effective without marked psychotomimetic effects in patients with cancer, and to result in less physical dependence than morphine.[29-31] Drugs in this class may offer special advantages to the management of pain from cancer.

Traditionally, the narcotic analgesics have been used to manage acute pain. Long-term use has been discouraged because of the development of tolerance, physical dependence, and psychological dependence.[32] Tolerance is a state in which escalating doses of drug are needed to maintain an analgesic effect. Physical dependence is characterized by the onset of acute symptoms and signs of withdrawal if the narcotic is suddenly stopped or a narcotic antagonist is administered. Psychological dependence, or addiction, is separate from physical dependence and tolerance and is a concomitant behavioral pattern of drug abuse characterized by a craving for the drug and overwhelming involvement in obtaining and using it.

Because of the misconception by both clinicians and patients that physical dependence and addiction (psychological dependence) are interchangeable terms, the use of narcotic analgesics in patients with acute or chronic pain remains inadequate at best. This overriding fear of addiction coupled with physicians' lack of knowledge about the clinicopharmacologic properties of narcotic agents further limits effective use of them.[33-35] However, advances in our understanding of endogenous opiates in pain modulation and the plight of the patient with pain from cancer have led to a reevaluation of the role of narcotic analgesics in the management of chronic pain.

The long-term use of narcotic analgesics, administered orally, to manage cancer pain was heralded by the English hospice movement[3,4] and has long been advocated in the care of patients dying from cancer.[32,36,37] Studies of the patterns of chronic narcotic drug use in patients with cancer and in those with other medical illnesses have demonstrated that tolerance and physical dependence occur but that psychological dependence (addiction) is rare.[38,39] This clinical experience with long-term narcotic drug use supports the concept that psychological dependence is separate from physical dependence.[10] Drug use is not the sole factor in the development of psychological dependence; psychological, social, and economic factors also play a part. This observation has been supported by studies of heroin use by U.S. military personnel in Vietnam.[40] The concept of "addiction" should be redefined in order to place the use of narcotic analgesics in perspective.[41]

Several reviews of oral and parenteral analgesics in the management of cancer pain provide guidelines for their use.[42-48] The American Medical Association[5] and the American College of Physicians[7] have outlined approaches to drug therapy in the management of severe chronic pain associated with advanced disease. Both groups have stressed the importance of providing adequate pain control and supportive care so that the patient can die relatively free of pain. They have also stressed the need to educate physicians and other health professionals in the care of patients with pain from cancer and in the use of narcotic analgesics.

Guidelines for the practical use of narcotic analgesics are presented in Table 4. Tables 5 and 6 list some of the important pharmacologic properties of the nonnarcotic and narcotic analgesics commonly used to

Table 4. Guidelines for the Use of Narcotic Analgesics in Pain Management.

1. Start with a specific drug for a specific type of pain.
2. Know the pharmacology of the drug prescribed.
   a. Duration of the analgesic effect.
   b. Pharmacokinetic properties of the drug.
   c. Equianalgesic doses for the drug and its route of administration (see Tables 5 and 6).
3. Adjust the route of administration to the patient's needs.
4. Administer the analgesic on a regular basis after initial titration of the dose.
5. Use drug combinations to provide additive analgesia and reduce side effects (e.g., nonsteroidal antiinflammatory drugs, antihistamine [hydroxyzine], amphetamine [Dexedrine]).
6. Avoid drug combinations that increase sedation without enhancing analgesia (e.g., benzodiazepine [diazepam] and phenothiazine [chlorpromazine]).
7. Anticipate and treat side effects.
   a. Sedation.
   b. Respiratory depression.
   c. Nausea and vomiting.
   d. Constipation.
8. Watch for the development of tolerance.
   a. Switch to an alternative narcotic analgesic.
   b. Start with one half the equianalgesic dose and titrate the dose for pain relief.
9. Prevent acute withdrawal.
   a. Taper drugs slowly.
   b. Use diluted doses of naloxone (0.4 mg in 10 ml of saline) to reverse respiratory depression in the physically dependent patient, and administer cautiously.
10. Do not use placebos to assess the nature of pain.
11. Anticipate and manage complications.
   a. Overdose.
   b. Multifocal myoclonus.
   c. Seizures.

treat cancer pain. The guidelines are based in part on clinicopharmacologic principles and in part on the empirical use of these drugs in clinical practice. They serve as a useful reference point, but there remains a tremendous need to develop scientifically based guidelines.

Several controversies have arisen in the use of narcotic analgesics, including the best choice of an analgesic (e.g., morphine, methadone, or heroin), the route and schedule of administration (fixed or as needed), and the risk of psychological dependence with long-term use.[49] Although resolution of these controversies awaits controlled repetitive dosage studies, some of the available data are briefly reviewed below.

There is no "best choice" of analgesic agent but rather a series of agents, such as those listed in Tables 5 and 6, that have been used effectively to manage cancer pain. Oral morphine is the most commonly used drug, but its availability for outpatient pain management is severely restricted in developed and developing countries. For patients who cannot tolerate morphine, there are useful alternative drugs. Choosing the drug according to the needs of the individual patient is the rule. There may be pharmacokinetic reasons to choose shorter-acting drugs, such as morphine or hydromorphone, over methadone or levorphanol, if they are given on a fixed schedule. Accumulation of a toxic active metabolite, normeperidine, limits the long-term use of meperidine. It is the knowledge of pharmacologic properties that directs the choice of a drug. Attention to these considerations will ensure effective use of drugs.

Lack of knowledge of the equianalgesic doses of drugs, when a switch is made from one medication to another or from one route of administration to another, is the most common cause of undermedication. Because cross-tolerance is not complete, patients who become tolerant to the analgesic effect of one narcotic can be given another narcotic to provide better analgesia.[36,45] One half the calculated equianalgesic dose of the new drug is recommended for titrating the starting dose. This calculation is based on clinical experience and suggests that the relative potency of some of the narcotic analgesics, specifically those with long plasma half-lives, may increase with repetitive doses.

Lack of attention to the pharmacokinetic profile has also limited the effective use of certain drugs. The plasma half-lives of the narcotic analgesics vary widely and do not correlate with their analgesic time courses. Both methadone, with a half-life of 15 to 30 hours, and levorphanol, with a half-life of 12 to 16 hours, produce analgesia for 4 to 6 hours.[50,51] With repeated doses, these drugs accumulate in plasma and can result in excessive sedation and respiratory depression.[52,53] It is necessary to adjust the dose and schedule according to the plasma half-life of the drug when it is introduced.[54,55]

Table 5. Oral Non-narcotic and Narcotic Analgesics for Mild to Moderate Pain.

	Equianalgesic Dose (mg)*	Duration (hr)	Plasma Half-Life (hr)	Comments
Aspirin	650	4–6	3–5	Standard for non-narcotic comparisons; gastrointestinal and hematologic effects limit use in patients with cancer
Acetaminophen	650	4–6	1–4	Weak antiinflammatory effects; safer than aspirin
Propoxyphene	65†	4–6	12	Biotransformed to potentially toxic metabolite norpropoxyphene; used in combination with non-narcotic analgesics
Codeine	32†	4–6	3	Biotransformed to morphine; available in combination with non-narcotic analgesics
Meperidine	50	4–6	3–4	Biotransformed to active toxic metabolite normeperidine; associated with myoclonus and seizures
Pentazocine	30	4–6	2–3	Psychotomimetic effects with escalation of dose; only available in combination with naloxone, aspirin, or acetaminophen (U.S.)

*Relative potency of drugs, as compared with that of aspirin, for mild to moderate pain.

†Some investigators have reported that a much larger dose (propoxyphene, 130 mg; codeine, 60 mg) is effective in patients with mild to moderate pain.

Medication should be administered on a regular basis with the interval between doses based on the duration of the analgesic effect. The pharmacologic objective is to maintain the plasma level of the drug above a "minimal effective concentration for pain relief."[56] However, the time required to reach a steady state after repeated administration depends on the half-life of the drug, and full assessment of the analgesic efficacy of a drug regimen may thus take 24 hours, for a drug such as morphine, or up to five to seven days, for methadone.[54]

The use of a combination of drugs enables the physician to improve pain relief without escalation of the narcotic dose. Several combinations have been proved effective, including a narcotic plus a non-narcotic (600 mg of aspirin or acetaminophen[36] or 400 mg of ibuprofen[57]), a narcotic plus an antihistamine (100 mg of hydroxyzine given intramuscularly),[58] and a narcotic plus an amphetamine (10 mg of dextroamphetamine [Dexedrine] given intramuscularly).[59] Other drugs, which do not provide additive analgesia but are commonly employed in combination with narcotic agents, include diazepam, chlorpromazine, and cocaine.[60-62]

The Brompton Cocktail, which consists of varying doses of diacetylmorphine (heroin) or morphine, cocaine, phenothiazine, alcohol, and chloroform water, has been reported to control pain in 90 per cent of patients. Studies by Twycross have demonstrated that analgesic efficacy results from the narcotic alone and that morphine can be substituted for heroin. He has therefore advocated using oral narcotic solutions in titrated doses according to the needs of the individual patient rather than using cocktails.[3,63]

The route of drug administration must also be selected according to the needs of the patient. The oral route is most practical, but the oral bioavailability of drugs varies widely. Recent studies have helped to establish a kinetic basis for the rational use of oral morphine and methadone in patients with cancer,[55,64-66] and have demonstrated that oral heroin, although effective as an analgesic, is inefficient as a means of

Table 6. Oral and Parenteral Narcotic Analgesics for Severe Pain.

	Route*	Equianalgesic Dose (mg)†	Duration (hr)	Plasma Half-Life (hr)	Comments
Narcotic agonists					
Morphine	IM	10	4–6	2–3.5	Standard for comparison; also available in slow-release tablets
	PO	60	4–7		
Codeine	IM	130	4–6	3	Biotransformed to morphine; useful as initial narcotic analgesic
	PO	200‡	4–6		
Oxycodone	IM	15		—	Short acting; available alone or as 5-mg dose in combination with aspirin and acetaminophen
	PO	30	3–5		
Heroin	IM	5	4–5	0.5	Illegal in U.S.; high solubility for parenteral administration
	PO	60	4–5		
Levorphanol (Levo-Dromoran)	IM	2	4–6	12–16	Good oral potency, requires careful titration in initial dosing because of drug accumulation
	PO	4	4–7		
Hydromorphone (Dilaudid)	IM	1.5	4–5	2–3	Available in high-potency injectable form (10 mg/ml) for cachectic patients and as rectal suppositories; more soluble than morphine
	PO	7.5	4–6		
Oxymorphone (Numorphan)	IM	1	4–6	2–3	Available in parenteral and rectal-suppository forms only
	PR	10	4–6		
Meperidine (Demerol)	IM	75	4–5	3–4 normeperidine	Contraindicated in patients with renal disease; accumulation of active toxic metabolite normeperidine produces CNS excitation
	PO	300‡	4–6	12–16	
Methadone (Dolophine)	IM	10		15–30	Good oral potency; requires careful titration of the initial dose to avoid drug accumulation
	PO	20			
Mixed agonist–antagonist drugs					
Pentazocine (Talwin)	IM	60	4–6	2–3	Limited use for cancer pain; psychotomimetic effects with dose escalation; available only in combination with naloxone, aspirin, or acetaminophen; may precipitate withdrawal in physically dependent patients
	PO	180‡	4–7		
Nalbuphine (Nubain)	IM	10	4–6	5	Not available orally; less severe psychotomimetic effects than pentazocine; may precipitate withdrawal in physically dependent patients
	PO	—			
Butorphanol (Stadol)	IM	2	4–6	2.5–3.5	Not available orally; produces psychotomimetic effects; may precipitate withdrawal in physically dependent patients
	PO	—			
Partial agonists					
Buprenorphine (Temgesic)	IM	0.4	4–6	?	Not available in U.S.; no psychotomimetic effects; may precipitate withdrawal in tolerant patients
	SL	0.8	5–6		

*IM denotes intramuscular, PO oral, PR rectal, and SL sublingual.

†Based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route. For patients without prior narcotic exposure, the recommended oral starting dose is 30 mg for morphine, 5 mg for methadone, 2 mg for levorphanol, and 4 mg for hydromorphone.

‡The recommended starting doses for these drugs are listed in Table 5.

delivering morphine.[67] Several novel methods and routes of administration have been developed to maximize pharmacologic effects and to minimize undesirable effects associated with standard methods — e.g., slow-release morphine tablets that are effective for 8 to 12 hours. Novel routes under investigation include intranasal, transdermal, and sublingual drug administration. The advantage of these routes is that they avoid drug metabolism by the liver (presystemic clearance), which substantially reduces the oral potency of morphine and some of the other narcotics. These alternative routes offer a special advantage, particularly in the patient with gastrointestinal obstruction, limited venous access, or reduced muscle mass. To date, only one drug, buprenorphine, is produced in a sublingual form, but it is not available in the United States.

Continuous infusions of narcotics by intravenous and subcutaneous routes have been employed to meet the needs of select populations of patients with cancer.[68-71] Although the indications for these techniques, their limitations, and their efficacy have not been fully assessed and the pharmacokinetic basis for their use remains undefined, their clinical use is widespread and expanding. The inability to predict an ideal maintenance infusion rate and to accommodate differences among patients makes it difficult to use these techniques.[72] The intravenous or oral equianalgesic doses are not known for many of the drugs. When a switch is made from the intramuscular route to continuous intravenous infusions, the starting dose is calculated as the equivalent morphine dose for a 24-hour period. This calculation is based on clinical experience, not controlled studies.[47]

Epidural and intrathecal administration of narcotics is based on the demonstration of opiate receptors in the dorsal horn and suppression of spinothalamic-tract neurons to noxious stimuli by opiates applied to the spinal cord.[73-78] Localized selective analgesia is produced without motor blockade. This approach minimizes the distribution of drugs to receptors in the brain stem and cerebral hemispheres, avoiding the side effects of systemic administration. The clinical efficacy of continuous infusions by this route, using the Infusaid pump, has been studied in patients with pain from cancer. The clinical and pharmacokinetic data demonstrate that profound analgesia can be produced with small doses of morphine. Because the dose and subsequent systemic uptake are much higher with epidural administration, the intrathecal route has been advocated. However, both epidural and intrathecal administration are associated with rostral redistribution of drug and central side effects. Also, tolerance occurs and is most problematic in the patient with progressive disease. Considerable cross-tolerance is induced by systemic narcotics, making it difficult to determine the proper timing for use of these techniques in the management of pain from cancer. Intraventricular administration of narcotics in patients with cancer has also been shown to provide profound analgesia when small doses of drug are administered through an Ommaya reservoir.[79]

As noted above, tolerance occurs with long-term administration in patients with progressive disease, but increased doses of drug continue to produce analgesia, suggesting that with the narcotic agonist drugs there is no limit to tolerance. Tolerance of each of the effects of the narcotics occurs at a different rate. Switching to an alternative narcotic, adding non-narcotic agents, and employing neurosurgical and anesthetic approaches are methods commonly used to manage pain in the patient with a tolerance to a particular narcotic agent.

These guidelines notwithstanding, the management of pain with analgesics remains difficult. Much of the difficulty encountered arises from differences in the responses of individual patients to the same dose of drug. Kaiko and colleagues have described some of the sources of variation in the responses of patients with cancer to morphine and the need for dose adjustment on the basis of age.[80,81] The efficacy of such drugs is based on an understanding of their clinicopharmacologic properties and improved methods to manage their side effects. Effective use of narcotic agents is now possible because of the development of specific and sensitive techniques to quantitate drugs in biofluids, the availability of well-defined clinical methods to measure the pain response, and the application of pharmacokinetic and pharmacodynamic models to relate plasma concentrations of narcotics to analgesic effects.[82,83] Recent studies demonstrate that equianalgesic doses of heroin are comparable to morphine in their analgesic effect, side effects, and influence on mood. These studies refute anecdotal reports of heroin's superiority.[84] Studies of repeated meperidine administration in patients with cancer have demonstrated that central nervous system hyperirritability results from accumulation of the active toxic metabolite, normeperidine.[85]

Adjuvant Analgesic Drugs

Adjuvant analgesic agents constitute a third group of drugs used to treat patients with pain from cancer.[86,87] This group includes several different categories of drugs, such as anticonvulsant agents,[88] phenothiazines,[89] butyrophenones,[90] tricyclic antidepressants,[91,92] antihistamines, amphetamines, and steroids[93,94] and levodopa.[95] These drugs produce analgesia in certain painful states by mechanisms not clearly established and not directly related to the opiate receptor system. Clinical interest in their use has developed from a greater understanding of the neuropharmacologic characteristics of pain and the ability of these drugs to enhance or block neurotransmitter function. In some instances, analgesic effects have been established in controlled clinical trials, such as the use of amitriptyline in postherpetic neuralgia,[91] but for most of these drugs, anecdotal data or clinical surveys provide the

rationale for their use, which is controversial at best. Although these drugs are commonly used in patients with pain from cancer, the evidence suggests that they are not as effective as narcotic analgesics in relieving pain. Adjuvant analgesic drugs have been developed and released for clinical indications other than pain relief.

Anesthetic Approaches

These approaches are most useful in treating patients with well-defined localized pain from tumor infiltration. Short-acting and long-acting anesthetics are used for temporary and diagnostic nerve blocks, whereas phenol, alcohol, and freezing (cryoanalgesia) are the common neurolytic agents used for permanent blocks.[96-99] The principal pathologic effect produced by these agents is demyelination, with secondary nerve degeneration. Local freezing causes a loss in nerve function, which reportedly lasts for several weeks only.[99] A permanent nerve block is performed if a temporary block has demonstrated efficacy. The most common indications for nerve block are listed in Table 3. The limitations of these procedures are that each peripheral nerve subserves sensory function over multiple levels, requiring multiple nerves to be blocked for adequate pain control. Similarly, epidural and intrathecal nerve blocks with neurolytic agents can produce motor weakness and autonomic dysfunction. The techniques, indications, and diluent and concentration of neurolytic agents vary from investigator to investigator, with satisfactory results reported in 22 to 80 per cent of patients and permanent side effects, such as urinary or rectal incontinence, motor weakness, or paresthesias, in 1 to 13 per cent.[96-102] However, the use of autonomic nerve blocks, such as celiac-plexus block, to manage midabdominal pain associated with carcinoma of the pancreas is very effective in 60 per cent of patients and is often the procedure of choice in such patients.[101]

Intermittent or continuous epidural infusions of local anesthetics have been used for temporary management of the difficult pain syndromes involving the lumbosacral plexus and sacrum. By varying the amount and concentration of the local anesthetic delivered continuously by an infusion pump or intermittently by a subcutaneously implanted reservoir attached to a catheter placed in the epidural space, pain relief can be achieved without interruption of motor or autonomic function.[103] The advantage of this method is that it does not result in cross-tolerance with opiate analgesia, and temporary use of epidural infusions allows for a reduction in the amount of systemic opiate drugs, partially reversing tolerance. This is a useful preliminary approach to reduce tolerance when spinal opiate analgesia is under consideration as a therapeutic approach.

Two anesthetic approaches used to manage diffuse pain are chemical hypophysectomy and intermittent inhalation therapy with nitrous oxide. Chemical hypophysectomy, which involves the injection of alcohol into the sella turcica under radiologic supervision, is used to control pain in patients with widespread bony metastases. Initial studies reported dramatic pain relief in 60 per cent of 600 patients, but more recent studies report relief in 35 to 74 per cent of patients.[104,105] The mechanism of analgesia may be related in part to the tracking of alcohol up the pituitary stalk and the consequent disruption of the hypothalamic–thalamic endorphinergic pain pathway. The lack of detailed clinical data and information on the endocrine status of such patients limits critical assessment of the technique, and in many patients pain relief occurs independently of tumor regression.

Nitrous oxide is used to manage chronic pain from tumor progression or pain in the dying patient.[106] It is administered in oxygen through a nonrebreathing face mask, with concentrations ranging from 25 to 75 per cent, often in combination with systemic narcotics. Patients can remain alert during its use. It is most useful in managing acute incident pain and procedure-related pain.

Lastly, trigger-point injections,[107] although considered an anesthetic procedure, are commonly used in clinical practice and require no special expertise. A focal injection of saline or local anesthetic into a painful muscle joint provides dramatic relief. However, a careful assessment of the nature of the pain should be undertaken.

Neurosurgical Approaches

At present, cordotomy and placement of epidural, intrathecal, and intraventricular catheters for narcotic drug delivery are the most common neurosurgical procedures performed for pain relief (Table 2).[108-113] A cordotomy involves the interruption of the anterior lateral spinothalamic tract in the cervical or thoracic region. It may be performed as a percutaneous stereotactic procedure or by an open surgical approach. It is most useful in managing unilateral pain below the waist. Initial complications include paresis in 5 per cent of patients, ataxia in 20 per cent, and urinary dysfunction in 10 per cent, with late complications occurring in only 5 per cent. Although initial pain relief from cordotomy occurs in 90 per cent of patients, this figure drops to 80 per cent at three months, and at the end of one year approximately 40 per cent of patients report a return of pain. Another limiting factor in the success of both open and percutaneous cordotomies is that pain develops on the side opposite the cordotomy site in 7 to 10 per cent of patients; even more distressing, in a comparable number of patients, pain previously unrecognized at another site becomes as intractable as the pain for which the cordotomy was performed. This is one of the most common causes for the failure of cordotomy and explains the limited usefulness of the procedure in patients with diffuse pain.

Each of the other neurosurgical procedures involves either sectioning or stimulation of the peripheral

nerves, spinal cord, brain stem, or thalamus. These are specialized procedures requiring neurosurgical expertise, and must often be performed at special centers.

Behavioral Approaches

Behavioral approaches, including relaxation training, biofeedback and cognitive and behavioral training, hypnosis, and music therapy, have been integrated into the management of cancer pain.[116-121] The major goal of these interventions is to promote an increased sense of control by reducing the hopelessness and helplessness that many patients with pain from cancer experience. These techniques also serve as a calming diversion of attention, breaking the pain–anxiety–tension cycle. The effectiveness of any one of these techniques, as compared with another or with standard medical or surgical therapy, is unknown, and few controlled studies have been performed. Patients are taught these techniques and then use them independently. Relaxation training can be given by all health care professionals, whereas other approaches require biophysical instrumentation or more specialized skills. Cognitive and behavioral training provides patients with a variety of strategies to divert their attention away from pain, facilitate their tolerance of pain, and increase their perceived self-control and adaptive functioning.

Music therapy has been used in hospitals and hospice settings either alone or in combination with relaxation training and hypnosis to augment the effects of these techniques.[119] Hypnosis has been studied the most extensively and has been widely used in the treatment of acute and chronic cancer pain.[120,121] Studies report that 50 per cent of patients may obtain some pain relief, yet indicate that there is no single effective hypnotic procedure.

In general, these behavioral techniques reduce pain by means of mechanisms that are in part related to their ability to modulate the affective response to painful stimuli. Studies have demonstrated that analgesia induced by hypnosis is not mediated by the endogenous opiate system, because it is not reversed by naloxone.[122]

Supportive Care

Numerous models of supportive care have stressed the importance of pain control for the patient at home. Inadequate control of pain in the outpatient is a common cause for readmission to the hospital. Specific guidelines for managing cancer pain at home include education of patients, their families, and health care professionals in the proper use of analgesics; 24-hour availability of a physician or a nurse with expertise in pain management to adjust drug doses; adequate drug supplies for alternative routes of administration, such as the parenteral route; and education in the use of naloxone to reverse opiate-induced respiratory depression.

These approaches, coupled with psychological support for patients and their families and integration of social services, can give the patient with pain the option to remain at home.[3,4,123,124]

Summary

Pain is one of the most feared consequences of cancer. Control of pain from cancer should be possible with the approaches discussed above. Changing attitudes toward the effective use of narcotic analgesics, the development of novel routes and methods of administration, and a clinical approach based on scientific principles and humane care offer the promise of improved management of pain in patients with cancer.

I am indebted to Dr. Raymond W. Houde for information on the equianalgesic doses of non-narcotic and narcotic analgesics and for his critical review of the manuscript, and to Mary Callaway for assistance in the preparation of the manuscript.

References

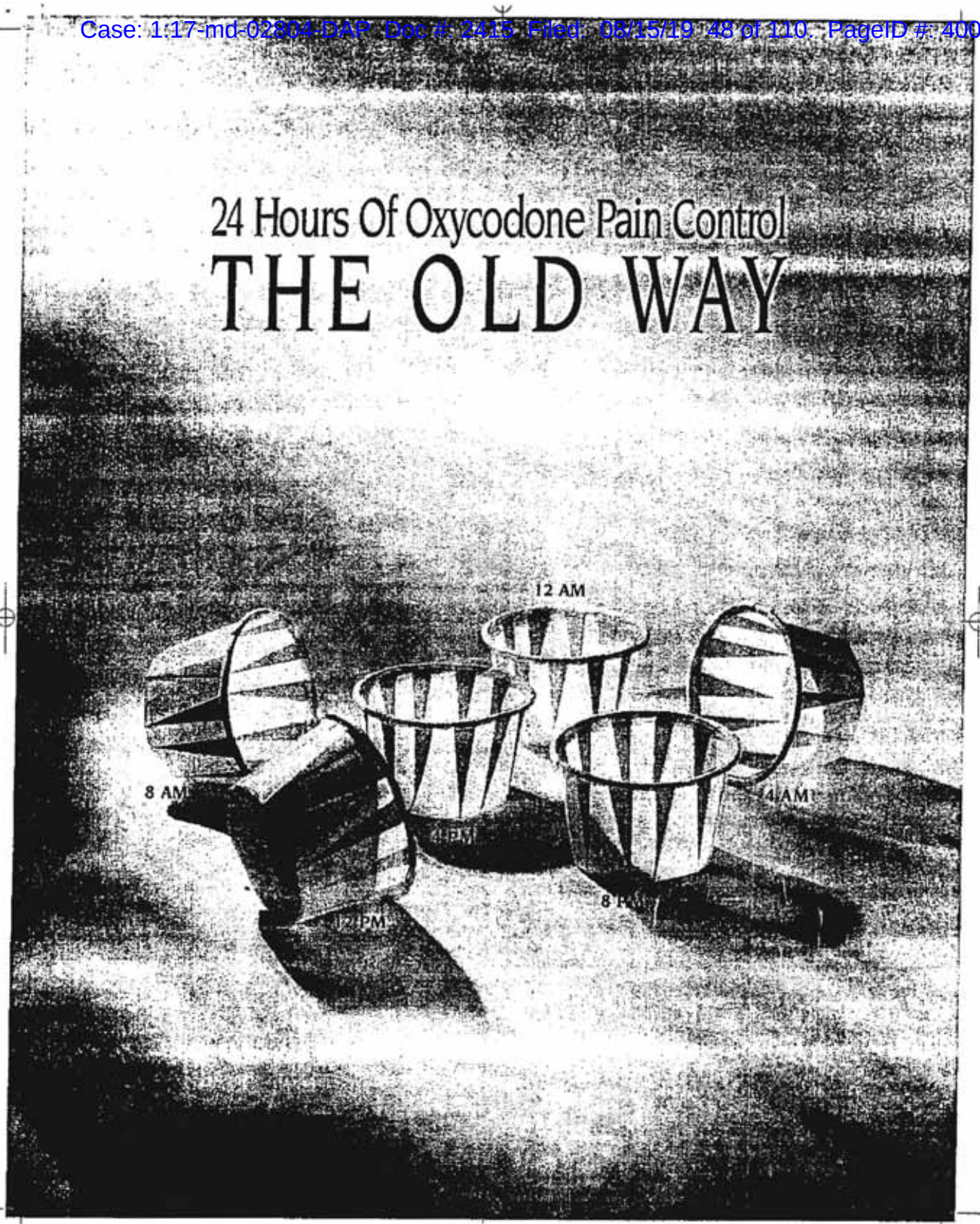
1. Payne R, Foley KM. Advances in the management of cancer pain. Cancer Treat Rep 1984; 68:173-83.
2. Bonica JJ. Importance of the problem. In: Bonica JJ, Ventafridda V, Fink RB, Jones LE, Loeser JD, eds. Advances in pain research and therapy. Vol. 2. New York: Raven Press, 1979:1-12.
3. Twycross RG, Lack SA. Symptom control in far advanced cancer: pain relief. London: Pitman, 1984.
4. Saunders CM. The management of terminal illness. London: Edward Arnold, 1967.
5. Foley KM. The management of pain of malignant origin. In: Tyler HR, Dawson DM, eds. Current neurology. Boston: Houghton Mifflin, 1979: 279-302.
6. McGivney WT, Crooks GM, eds. The care of patients with severe chronic pain in terminal illness. JAMA 1984; 251:1182-8.
7. Health and Public Policy Committee, American College of Physicians. Drug therapy for severe chronic pain in terminal illness. Ann Intern Med 1983; 99:870-3.
8. Twycross RG, Fairfield S. Pain in far-advanced cancer. Pain 1982; 14:303-10.
9. Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. Cancer 1982; 50:1913-8.
10. Kanner RM, Foley KM. Patterns of narcotic drug use in a cancer pain clinic. Ann NY Acad Sci 1981; 362:161-72.
11. Cleeland CS. The impact of pain on patients with cancer. Cancer 1984; 54:2635-41.
12. Foley KM. Pain syndromes in patients with cancer. In: Bonica JJ, Ventafridda V, Fink RB, Jones LE, Loeser JD, eds. Advances in pain research and therapy. Vol. 2. New York: Raven Press, 1979:59-75.
13. Swerdlow M, Stjernswärd J. Cancer pain relief — an urgent problem. World Health Forum 1982; 3:325-30.
14. Basbaum AI, Fields HL. Endogenous pain control mechanisms: review and hypothesis. Ann Neurol 1978; 4:451-62.
15. Sternbach RA. Pain patients: traits and treatment. New York: Academic Press, 1974.
16. IASP Subcommittee on Taxonomy Pain Terms: a list with definitions and notes on usage. Pain 1979; 6:249-52.
17. Spiegel D, Bloom JR. Pain in metastatic breast cancer. Cancer 1983; 52:341-5.
18. Fultz JM, Senay EC. Guidelines for management of hospitalized narcotic addicts. Ann Intern Med 1975; 82:815-8.
19. Bonica JJ. The management of pain. Philadelphia: Lea & Febiger, 1953.
20. Tasker RR, Tsuda T, Hawrylyshyn P. Clinical neurophysiological investigation of deafferentation pain. In: Bonica JJ, Lindblom U, Iggo A, eds. Advances in pain research and therapy. Vol. 5. New York: Raven Press, 1981:713-38.
21. Foley KM. Clinical assessment of cancer pain. Acta Anesthesiol Scand [Suppl] 1982; 74:91-6.
22. Twycross RG, Ventafridda V, eds. The continuing care of terminal cancer patients. Oxford: Pergamon Press, 1980.
23. Gerbershagen HU. Nonnarcotic analgesics. In: Bonica JJ, Ventafridda V, Fink RB, Jones LE, Loeser JD, eds. Advances in pain research and therapy. Vol. 2. New York: Raven Press, 1979:255-73.

24. Kantor TG. Control of pain by nonsteroidal anti-inflammatory drugs. Med Clin North Am 1982; 66:1053-9.
25. Moertel GG. Treatment of cancer pain with orally administered medications. JAMA 1980; 244:2448-50.
26. Brodie GN. Indomethacin and bone pain. Lancet 1974; 2:1160.
27. Brereton HD, Halushka PV, Alexander RW, Mason DM, Keiser HR, DeVita VT Jr. Indomethacin-responsive hypercalcemia in a patient with renal-cell adenocarcinoma. N Engl J Med 1974; 291:83-5.
28. Galasko CSB. Mechanisms of bone destruction in the development of skeletal metastases. Nature 1976; 263:507-10.
29. Houde RW. Analgesic effectiveness of the narcotic agonist-antagonists. Br J Clin Pharmacol 1979; 7:297S-308S.
30. Robbie DS. A trial of sublingual buprenorphine in cancer pain. Br J Clin Pharmacol 1979; 7:315S-85S.
31. Ventafridda V, DeConno F, Guarise G, et al. Chronic analgesic study on buprenorphine action in cancer pain — comparison with pentazocine. Drug Res 1983; 4:587-90.
32. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. 6th ed. New York: Macmillan, 1980:494-534.
33. Marks RM, Sachar EJ. Undertreatment of medical inpatients with narcotic analgesics. Ann Intern Med 1973; 78:173-81.
34. Charap AD. The knowledge, attitudes and experience of medical personnel treating pain in the terminally ill. Mt Sinai J Med 1978; 45: 561-80.
35. Sriwatanakul K, Weis OF, Alloza JL, Kelvie W, Weintraub M, Lasagna L. Analysis of narcotic analgesic usage in the treatment of postoperative pain. JAMA 1983; 250:926-9.
36. Houde RW, Wallenstein SL, Beaver WT. Evaluation of analgesics in patients with cancer pain. In: Lasagna L, ed. International encyclopedia of pharmacology and therapeutics. Section 6. Clinical pharmacology. Vol. 1. New York: Pergamon Press, 1966:59-97.
37. Paulsbock BZ. William Heberden and opium — some relief to all. N Engl J Med 1983; 308:53-5.
38. Angell M. The quality of mercy. N Engl J Med 1982; 306:98-9.
39. Porter J, Jick H. Addiction rare in patients treated with narcotics. N Engl J Med 1980; 302:123.
40. Robins LN, David DH, Nurco DN. How permanent was Vietnam drug addiction. Am J Public Health 1974; 64:38-43.
41. Newman RG. The need to redefine "addiction." N Engl J Med 1983; 308:1096-8.
42. Beaver WT. Management of cancer pain with parenteral medication. JAMA 1980; 244:2653-7.
43. Shimm DS, Logue GL, Maltbie AA, Dugan S. Medical management of chronic cancer pain. JAMA 1979; 241:2408-12.
44. Inturrisi CE. Narcotic drugs. Med Clin North Am 1982; 66:1061-71.
45. Inturrisi CE, Foley KM. Narcotic analgesics in the management of pain. In: Kuhar M, Pasternak G, eds. Analgesics: neurochemical, behavioral and clinical perspectives. New York: Raven Press, 1984:257-87.
46. Houde RW, Wallenstein SL, Beavers WT. Clinical measurement of pain. In: deStevens G, ed. Analgesics. New York: Academic Press, 1965:75-122.
47. Foley KM. The practical use of narcotic analgesics. Med Clin North Am 1982; 66:1091-104.
48. Rane A, Säwe J, Dahlström B, Paalzow L, Kager L. Pharmacological treatment of cancer pain with special reference to the oral use of morphine. Acta Anaesthesiol Scand [Suppl] 1982; 74:97-103.
49. Foley KM. Current controversies in the management of cancer pain. In: NIDA Res Monograph Series 1981; 36:169-81.
50. Inturrisi CE, Verebely K. Disposition of methadone in man after a single oral dose. Clin Pharmacol Ther 1972; 13:923-30.
51. Dixon R, Crews T, Mohacsi C, Inturrisi C, Foley K. Levorphanol: radioimmunoassay and plasma concentration profiles in dog and man. Res Commun Chem Pathol Pharmacol 1980; 29:535-47.
52. Ettinger DS, Vitale PJ, Trump DL. Important clinical pharmacologic considerations in the use of methadone in cancer patients. Cancer Treat Rep 1979; 63:457-9.
53. Symonds P. Methadone and the elderly. Br Med J 1977; 1:512.
54. Breivik H, Rennemo F. Clinical evaluation of combined treatment with methadone and psychotropic drugs in cancer patients. Acta Anaesthesiol Scand [Suppl] 1982; 74:135-40.
55. Säwe J, Hansen J, Ginman C, et al. Patient-controlled dose regimen for methadone for chronic cancer pain. Br Med J 1981; 282:771-3.
56. Paalzow LK. Pharmacokinetic aspects of optimal pain treatment. Acta Anaesthesiol Scand [Suppl] 1982; 74:37-43.
57. Ferrer-Brechner T, Ganz P. Combination therapy with ibuprofen and methadone for chronic cancer pain. Am J Med 1984; 77:78-83.
58. Beaver WT, Feise G. Comparison of analgesic effects of morphine sulfate, hydroxyzine and their combination in patients with postoperative pain. In: Bonica JJ, Albe-Fessard D, eds. Advances in pain research and therapy. Vol. 1. New York: Raven Press, 1976:553-7.
59. Forrest WH Jr, Brown BW Jr, Brown CR, et al. Dextroamphetamine with morphine for the treatment of postoperative pain. N Engl J Med 1977; 296:712-5.
60. Singh PN, Sharma P, Gupta PK, Pandey K. Chemical evaluation of diazepam for relief of postoperative pain. Br J Anaesth 1981; 53:831-5.
61. Dundee JW, Moore J. The myth of phenothiazine potentiation. Anaesthesia 1961; 16:95-6.
62. Twycross R. Value of cocaine in opiate-containing elixirs. Br Med J 1977; 2:1348.
63. Twycross RG. Clinical experience with diamorphine in advanced malignant disease. Int J Clin Pharmacol Ther Toxicol 1974; 9:184-98.
64. Säwe J, Dahlström B, Paalzow L, Rane A. Morphine kinetics in cancer patients. Clin Pharmacol Ther 1981; 30:629-35.
65. Säwe J, Dahlström B, Rane A. Steady-state kinetics and analgesic effect of oral morphine in cancer patients. Eur J Clin Pharmacol 1983; 24: 537-42.
66. Säwe J, Svensson JO, Rane A. Morphine metabolism in cancer patients on increasing oral doses — no evidence for autoinduction or dose-dependence. Br J Clin Pharmacol 1983; 16:85-93.
67. Inturrisi CE, Max MB, Foley KM, Schultz M, Shin S-U, Houde RW. The pharmacokinetics of heroin in patients with chronic pain. N Engl J Med 1984; 210:1213-7.
68. DeChristoforo R, Corden BJ, Hood JC, Narang PK, Magrath IT. High-dose morphine infusion complicated by chlorobutanol-induced somnolence. Ann Intern Med 1983; 98:335-6.
69. Fraser DG. Intravenous morphine infusion for chronic pain. Ann Intern Med 1980; 93:781-2.
70. Miser AW, Miser JS, Clark BS. Continuous intravenous infusion of morphine sulfate for control of severe pain in children with terminal malignancy. J Pediatr 1980; 96:930-2.
71. Campbell CF, Mason JB, Weiler JM. Continuous subcutaneous infusion of morphine for the pain of terminal malignancy. Ann Intern Med 1983; 98:51-2.
72. Graves DA, Foster TS, Batenhorst RL, Bennett RL, Baumann TJ. Patient controlled analgesia. Ann Intern Med 1983; 99:360-6.
73. Yaksh TL. Spinal opiate analgesia: characteristics and principles of action. Pain 1981; 11:293-346.
74. Coombs DW, Saunders RL, Gaylor MS, Pageau MG. Epidural narcotic infusion reservoir: implantation technique and efficacy. Anesthesiology 1982; 56:469-73.
75. Coombs DW, Saunders RL, Gaylor MS, et al. Relief of continuous chronic pain by intraspinal narcotics infusion via an implanted reservoir. JAMA 1983; 250:2336-9.
76. Onofrio BM, Yaksh TL, Arnold PG. Continuous low-dose intrathecal morphine in the treatment of chronic pain of malignant origin. Mayo Clin Proc 1981; 56:516-20.
77. Poletti CE, Cohen AM, Todd DP, Ojemann RG, Sweet WH, Zervas NT. Cancer pain relieved by long-term epidural morphine with permanent indwelling systems for self-administration. J Neurosurg 1981; 55:581-4.
78. Greenberg HS, Taren J, Ensminger WD, Doan K. Benefit from and tolerance to continuous intrathecal infusion of morphine for intractable cancer pain. J Neurosurg 1982; 57:360-4.
79. Lobato RD, Madrid JL, Fatela LV, Rivas JJ, Reig E, Lamas E. Intraventricular morphine for control of pain in terminal cancer patients. J Neurosurg 1983; 59:627-33.
80. Kaiko RF. Age and morphine analgesia in cancer patients with postoperative pain. Clin Pharmacol Ther 1980; 28:823-6.
81. Kaiko RF, Wallenstein SL, Rogers AG, Houde RW. Sources of variation in analgesic responses in cancer patients with chronic pain receiving morphine. Pain 1983; 15:191-200.
82. Houde RW. Methods for measuring clinical pain in humans. Acta Anaesthesiol Scand [Suppl] 1982; 74:25-9.
83. Colburn WA. Simultaneous pharmacokinetic and pharmacodynamic modeling. J Pharmacokinet Biopharm 1981; 9:367-88.
84. Kaiko RF, Wallenstein SL, Rogers AG, Grabinski PY, Houde RW. Analgesic and mood effects of heroin and morphine in cancer patients with postoperative pain. N Engl J Med 1981; 304:1501-5.
85. Kaiko RF, Foley KM, Grabinski PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. Ann Neurol 1983; 13: 180-5.
86. Halpern LW. Psychotropics, ataractics and related drugs. In: Bonica JJ, Ventafridda V, eds. Advances in pain research and therapy. Vol. 2. New York: Raven Press, 1979:275-83.
87. Hanks GW. Psychotropic drugs. Clinics Oncol 1984; 3:135-51.
88. Swerdlow M. Anticonvulsant drugs and chronic pain. Clin Neuropharmacol 1984; 7:51-82.
89. Beaver WT, Wallenstein SL, Houde RW, Rogers A. A comparison of the analgesic effect of methotrimeprazine and morphine in patients with cancer. Clin Pharmacol Ther 1966; 7:436-46.
90. Hanks GW, Thomas PJ, Trueman T, Weeks E. The myth of haloperidol potentiation. Lancet 1983; 2:523-4.

91. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. Neurology (NY) 1982; 32:671-3.
92. Walsh TD. Antidepressants and chronic pain. Clin Neuropharmacol 1983; 6:271-95.
93. Schell HW. The risk of adrenal corticosteroid therapy with far-advanced cancer. Am J Med Sci 1966; 252:641-9.
94. *Idem*. Adrenal corticosteroid therapy in far-advanced cancer. Geriatrics 1972; 27:131-41.
95. Minton JP. The response of breast cancer patients with bone pain to L-dopa. Cancer 1974; 33:358-63.
96. Cousins MJ, Bridenbaugh PO, eds. Neural blockade. Philadelphia: JB Lippincott, 1980.
97. Arnér S. The role of nerve blocks in the treatment of cancer pain. Acta Anaesth Scand [Suppl] 1982; 74:104-8.
98. Brechner VL, Ferrer-Brechner T, Allen GD. Anesthetic measures in management of pain associated with malignancy. Semin Oncol 1977; 4:99-108.
99. Lloyd JW, Barnard JDW, Glynn CJ. Cryoanalgesia: a new approach to pain relief. Lancet 1976; 2:932-4.
100. Swerdlow M. Spinal and peripheral neurolysis for managing Pancoast syndrome. In: Bonica JJ, Ventafridda V, Pagni CA, Jones LE, eds. Advances in pain research and therapy. Vol. 4. New York: Raven Press, 1982:135-44.
101. Moore DC. Role of nerve block in neurolytic solutions for pelvic visceral cancer pain. In: Bonica JJ, Ventafridda V, eds. Advances in pain research and therapy. Vol. 2. New York: Raven Press, 1979:593-6.
102. Ventafridda V, Martino G. Clinical evaluation of subarachnoid neurolytic blocks in intractable cancer pain. In: Bonica JJ, Albe-Fessard D, eds. Advances in pain research and therapy. Vol. 1. New York: Raven Press, 1976:699-703.
103. Piloo RN, Baker AR. Chronic pain control by means of an epidural catheter: report of a case with description of the method. Cancer 1976; 37:903-5.
104. Moricca G. Chemical hypophysectomy for cancer pain. In: Bonica JJ, ed. Advances in neurology. Vol. 4. New York: Raven Press, 1974: 707-14.
105. Miles J, Lipton S. Mode of action by which pituitary alcohol injection relieves pain. In: Bonica JJ, Albe-Fessard D, eds. Advances in pain research and therapy. Vol. 1. New York: Raven Press, 1976:867-9.
106. Fosburg MT, Crone RK. Nitrous oxide analgesia for refractory pain in the terminally ill. JAMA 1983; 250:511-3.
107. Travell J. Myofascial trigger points: clinical review. In: Bonica JJ, Albe-Fessard D, eds. Advances in pain research and therapy. Vol. 1. New York: Raven Press, 1976:919-26.
108. Friedberg SR. Neurosurgical treatment of pain caused by cancer. Med Clin North Am 1975; 59:481-5.
109. Ventafridda V, Sganzerla EP, Fochi C, et al. Transcutaneous nerve stimulation in cancer pain. In: Bonica JJ, Ventafridda V, eds. Advances in pain research and therapy. Vol. 2. New York: Raven Press, 1979:509-15.
110. Loeser JD. Dorsal column and peripheral nerve stimulation for relief of cancer pain. In: Bonica JJ, Ventafridda V, eds. Advances in pain research and therapy. Vol. 2. New York: Raven Press, 1979:499-507.
111. Meyerson BA. Central nervous stimulation for cancer pain: possible methods of manipulating the physiology of pain control. In: Bonica JJ, Ventafridda V, Pagni CA, Jones LE, eds. Advances in pain research and therapy. Vol. 4. New York: Raven Press, 1982:149-64.
112. Nathan PW. Pain in cancer: comparison of results of cordotomy and chemical rhizotomy. In: Fusek I, Kunc T, eds. Present limits of neurosurgery. Amsterdam: Excerpta Medica, 1972:513-6.
113. *Idem*. Results of antero-lateral cordotomy for pain in cancer. J Neurol Neurosurg Psychiatry 1963; 26:353-62.
114. Ventafridda V, DeConno F, Fochi C. Clinical percutaneous cordotomy. In: Bonica JJ, Ventafridda V, Pagni CA, Jones LE, eds. Advances in pain research and therapy. Vol. 4. New York: Raven Press, 1982:185-98.
115. Nashold BS, Ostdahl RH. Dorsal root entry zone lesions for pain relief. J Neurosurg 1979; 51:59-69.
116. Turk DC, Meichenbaum DH, Berman WH. Application of biofeedback for the regulation of pain: a critical review. Psychol Bull 1979; 86: 1322-38.
117. Chappell MN, Stevenson TI. Group psychological training in some organic conditions. Ment Hyg 1936; 20:588-97.
118. Rybstein-Blinchik E. Effects of different cognitive strategies on chronic pain experience. J Behav Med 1979; 2:93-101.
119. Munro S, Mount B. Music therapy in palliative care. Can Med Assoc J 1978; 119:1029-34.
120. Koerner ME. Using hypnosis to relieve pain of terminal cancer. Hypnosis Q 1977; 20:39-46.
121. Barber J, Gitelson J. Cancer pain: psychological management using hypnosis. Cancer 1980; 30:130-5.
122. Mayer DJ, Price DD. Central nervous system mechanisms of analgesia. Pain 1976; 2:379-404.
123. Meyers AR, Master RJ, Kirk EM, et al. Integrated care for the terminally ill: variations in the utilization of formal services. Gerontology 1983; 23:71-4.
124. Coyle N, Monzillo E, Loscalzo M, Farkas C, Massie MJ, Foley KM. A model of continuity of care for cancer patients with pain and neuro-oncologic complications. Cancer Nurs 1985; 8:111-9.

Indicates changes requested by DDMAC

Indicates change made by Purdue Pharma after initial DDMAC review


24 Hours Of Oxycodone Pain Control
THE OLD WAY
12 AM
8 AM
4 AM
12 PM
8 PM


24 Hours Of Oxycodone Pain Control
THE NEW WAY
8 AM
8 PM

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

New q12h OxyContin™ II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

larger

The one to start with. (A-T-C).*

- The logical "next step" for patients with persistent pain no longer tolerating or responding to nonopioids
- ~~Pain relief begins~~ Analgesic onset within 1 hour in most patients—pain control lasts 12 hours
- Less frequent dosing than with Percocet®, Vicodin®, or Tylenol® with Codeine

The one to stay with.

- No "ceiling" to analgesic efficacy—may be titrated upward when clinically necessary
- Patients avoid the added risk of gastric/hepatic/renal toxicity that can result from ~~high~~ maximal daily doses of ASA or APAP
- Excellent compliance, high degree of patient acceptability during clinical trials

Easy to live with.

- Convenient q12h schedule won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
- Common opioid side effects may be anticipated and effectively managed or prevented; many diminish over time for most patients, except for constipation

Easy to dose.

- Small, color-coded tablets are easy to identify and swallow ~~an important benefit for patients on multiple medications~~

Actual Size

- Variety of strengths permit precise titration to an effective dose
- Manage breakthrough or incident pain with IR oxycodone to avoid polypharmacy

larger

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids is overdosage-causing respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

including OxyContin;

OxyContin™
The longest-lasting oxycodone ever.

Around-the-clock

larger Please see accompanying professional prescribing information

EASY TO DOSE.

The goal of titration:

To effectively control pain with two or fewer rescue doses per day.

OxyContin Titration Guide

	OxyContin Tablets q12h dose	IR oxycodone dose for rescue	
10mg	10mg q12h	5mg	Titrate the dose if more than two rescue doses per day are needed.
10mg	20mg q12h	5mg	
10mg	30mg q12h	10mg	
20mg	40mg q12h	10mg	
20mg	60mg q12h	15mg	
40mg	80mg q12h	20mg	
40mg	120mg q12h	30mg	
	Continue titrating, if necessary, using the T•I•M•E principles below.		

Titrate patients every 1-2 days, if necessary.

Increase the dose by 25%-50%, if necessary; do not increase the dosing frequency.

Manage breakthrough pain with IR oxycodone at ¼ to ⅓ of the 12-hour OxyContin dose.

Elevate the OxyContin dose if more than two rescue doses are required per day.

For patients taking OxyContin 10mg q12h...

- The next titration step should be 20mg q12h
- Breakthrough pain should be managed with IR oxycodone 5mg

New q12h

OXYCONTIN™ II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

Please see accompanying prescribing information.

Easy to dose

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin™ EA

Starting on OxyContin.

Recommended initial dose for opioid-naive patients.

For around-the-clock pain:

OxyContin™ CII

10 mg q12h

If a nonopioid analgesic is being taken, it may be continued.

For supplemental analgesia:

Immediate-Release (IR) Oxycodone*

5 mg administered 1 hour before anticipated incident pain

5 mg administered ~~q3-4h prn~~ for breakthrough pain (if needed)

Note: If more than two rescue doses are needed per day, OxyContin should be titrated upward.

Converting to OxyContin.

Fixed-Combination Opioid/ Nonopioid Products → **OxyContin**

Dose of regular-strength products (eg, Percocet®, Percodan®, Tylox®, Vicodin®, Lortab®, Lorcet®, or Tylenol® With Codeine)	Recommended OxyContin conversion dose range	IR oxycodone rescue dose for breakthrough pain*
1-5 Tablets/Capsules/ Caplets per day	10-20 mg q12h	5 mg ~~q3-4h prn~~
6-9 Tablets/Capsules/ Caplets per day	20-30 mg q12h	5-10 mg ~~q3-4h prn~~
10-12 Tablets/Capsules/ Caplets per day	30-40 mg q12h	10 mg ~~q3-4h prn~~

Note: The nonopioid ingredient may be continued as a separate drug. Discontinue all other around-the-clock opioids when initiating OxyContin therapy.

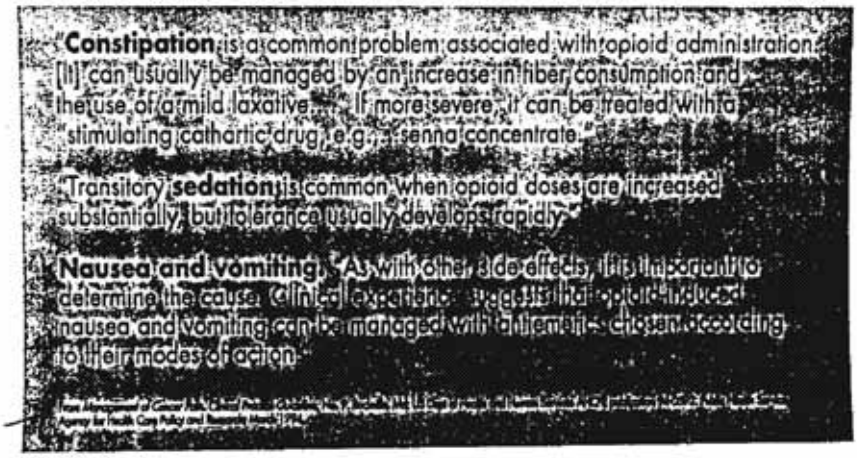
* See professional ~~prescribing~~ information for immediate-release oxycodone

Warning: Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. See WARNINGS and PRECAUTIONS sections in professional prescribing information.

16

EASY TO LIVE WITH.

The AHCPR, in *Management of Cancer Pain*, recommends that side effects be treated aggressively...



"**Constipation** is a common problem associated with opioid administration. [It] can usually be managed by an increase in fiber consumption and the use of a mild laxative. . . . If more severe, it can be treated with a stimulating cathartic drug, e.g., senna concentrate."

"Transitory **sedation** is common when opioid doses are increased substantially, but tolerance usually develops rapidly."

"**Nausea and vomiting.** As with other side effects, it is important to determine the cause. Clinical experience suggests that opioid-induced nausea and vomiting can be managed with antiemetic drugs according to their modes of action."

From Management of Cancer Pain Guideline. Agency for Health Care Policy and Research. March 1994.

larger

Easy to live with

New q12h

OXYCONTIN® (OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

larger [Warning—May be habit forming

larger [professional

15

THE ONE TO STAY WITH.

In cancer studies†...

- Titration enhanced efficacy of therapy—only 3.5% of cancer patients discontinued (due to inadequate pain control) when allowed to titrate and use rescue medication
- Patients were titrated as quickly and easily with OxyContin as with immediate-release oxycodone
- 92% of patients were titrated to stable pain control with OxyContin
- Average time to stable pain control was 2 days

† Data on file, Purdue Pharma L.P.

100% of OxyContin patients were dosed q12h

Easy to titrate

New q12h

OxyContin™ (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

Please see accompanying professional prescribing information.

13

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin™ EA

Common opioid side effects; many diminish over time, except for constipation

Adverse experiences reported over time by cancer patients (n=86)*

Drug-related ADE	Week 1 (%)^	Week 5 (%)^	Week 10 (%)^
Nausea	20	12	4
Sedation	14	8	8
Dry Mouth	9	0	0
Vomiting	8	7	0
Pruritus	7	0	0
Dizziness	5	5	0

*Percent of patients reporting ADE once or more during specified week of OxyContin therapy.

- The most serious risk associated with opioids is respiratory depression
- A significant decrease in the percent of patients reporting adverse events was seen between the first and last weeks of the study ($P<0.0001$)
- Most side effects diminished over time, even as daily doses increased — except for constipation
- Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness

*Caplan, Portis, Crighton, et al. Decrease in opioid-related adverse experiences (AE) during chronic therapy with controlled-release oxycodone (OxyCR) in cancer pain patients. Presented at the American Pain Society, November, 1995, Los Angeles, CA.

THE ONE TO STAY WITH.

A single-entity agent—dose not limited by ASA or APAP "ceilings."

Product (opioid/nonopioid ratio [mg])	Nonopioid Ingredient	Maximum Recommended Daily Dose of Nonopioid Ingredient: Goodman & Gilman[1]	Regimen Should Not Exceed...
OxyContin™	N/A	N/A	N/A
Percocet® (5/325)	APAP	4 g	12 tabs/day
Percodan® (5/325)	ASA	6 g	18 tabs/day
Tylox® (5/500)	APAP	4 g	8 tabs/day
Vicodin® (5/500)	APAP	4 g	8 tabs/day[2]
Vicodin® ES (7.5/750)	APAP	4 g	5 tabs/day[2]
Lorcet® HD (5/500)	APAP	4 g	8 tabs/day
Lorcet® (10/650)	APAP	4 g	6 tabs/day[2]
Lortab® (2.5/500)	APAP	4 g	8 tabs/day[2]
Lortab® (5/500)	APAP	4 g	8 tabs/day[2]
Lortab® (7.5/500)	APAP	4 g	6 tabs/day[2]
Lortab® ASA (5/500)	ASA	6 g	8 tabs/day[2]
Tylenol® with Codeine			
No. 2 (15/300)	APAP	4 g	13 tabs/day[3]
No. 3 (30/300)	APAP	4 g	12 tabs/day[3]
No. 4 (60/300)	APAP	4 g	6 tabs/day[3]

[1] *Management of Cancer Pain: Adults. Clinical Practice Guideline.* Quick Reference Guide for Clinicians. Rockville, Md: US Dept of Health and Human Services AHCPR publication 94-0593. Public Health Service, Agency for Health Care Policy and Research; March 1994.

[2] Kaplan, Portis, Croghan, et al. Decrease in opioid-related adverse experiences (AE) during chronic therapy with controlled-release oxycodone (OxyCR) in cancer pain patients. Presented at the American Pain Society, November, 1995, Los Angeles, CA.

[3] Insel PA. Analgesic-antipyretics and antiinflammatory agents: drugs employed in the treatment of rheumatoid arthritis and gout. In: Goodman LS, Gilman A, eds. *The Pharmacological Basis of Therapeutics.* New York, NY: McGraw Hill, Inc.; 1990:638-681.

[4] *Physicians' Desk Reference®.* 49th ed. Montvale, NJ: Medical Economics Data; 1995 (see respective product names).

larger

New q12h

OxyContin™ II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

larger **Warning**—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

larger Please see accompanying professional prescribing information.

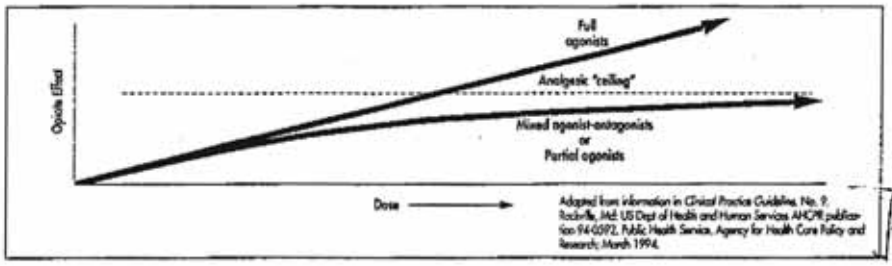
11

The one to stay with.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin™

No ceiling to analgesic efficacy.



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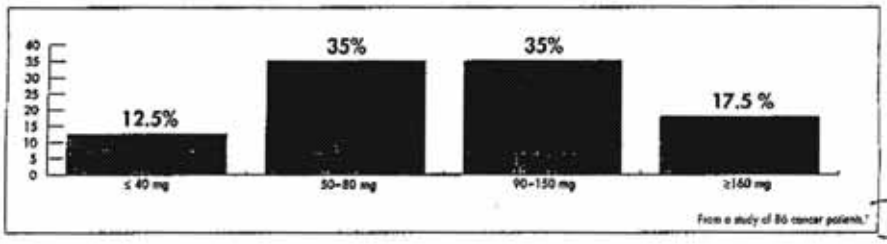
— With full agonists, such as oxycodone, "effectiveness with increasing doses is not limited by a 'ceiling'."*

OxyContin may be dosed upward as clinically necessary.

Percent of cancer patients receiving various daily doses of OxyContin at the end of a 12-week trial.



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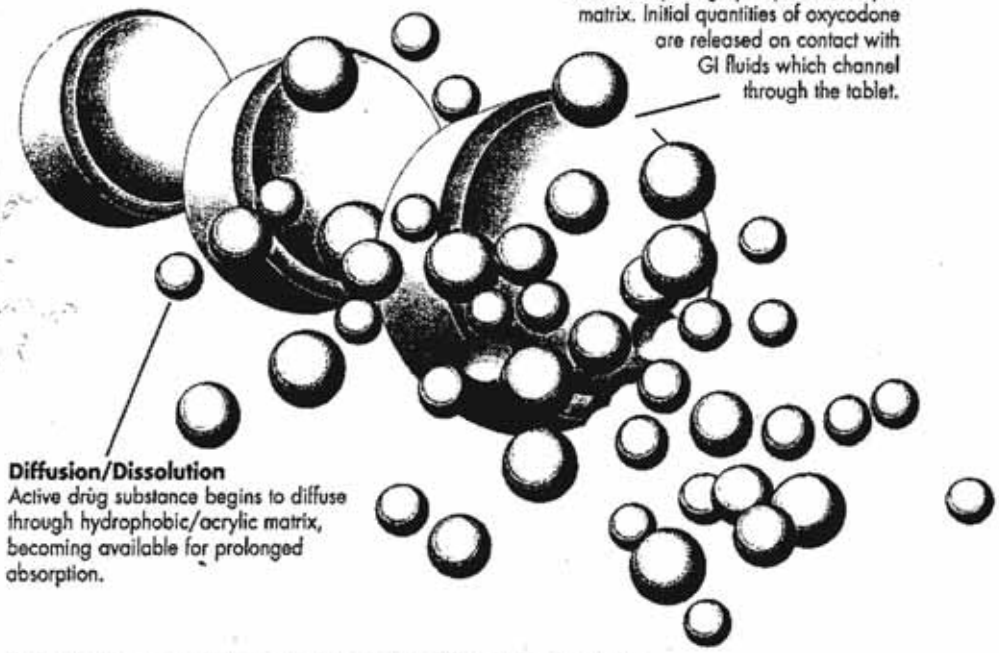
Ideal for long-term opioid therapy

— A single-entity oral agent—contains no APAP or ASA; allows independent coadministration and dosage adjustments with nonopioid of choice

ACROCONTIN® Delivery System.

The OxyContin™ CII (oxycodone HCl controlled-release) Tablets Dual Action Delivery System.



Special patented polymer/acrylic matrix of the delivery system renders OxyContin Tablets "pH independent," allowing uniform release within an acid environment (the stomach) or an alkaline environment (the intestines).

(A) *"pH independence" assures...*
- Minimal effect of stomach contents on absorption—bioavailability unaffected by food.

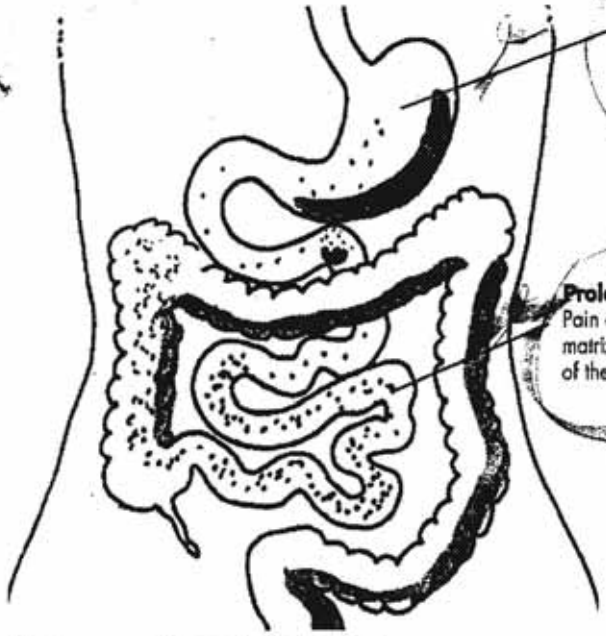
Please see accompanying ~~full~~ professional prescribing information. larger

bold — OxyContin tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

The 12-hour ACR

Improved Contin® delivery system allows both rapid and prolonged ~~absorption.~~ release



release
Rapid ~~absorption~~
~~Pain relief begins promptly.~~ Analgesic onset within 1 hour
as a portion of the active oxycodone is ~~rapidly~~ released and absorbed ~~quickly~~

release
Prolonged ~~absorption~~
Pain control continues as tablet matrix slowly releases the remainder of the oxycodone.

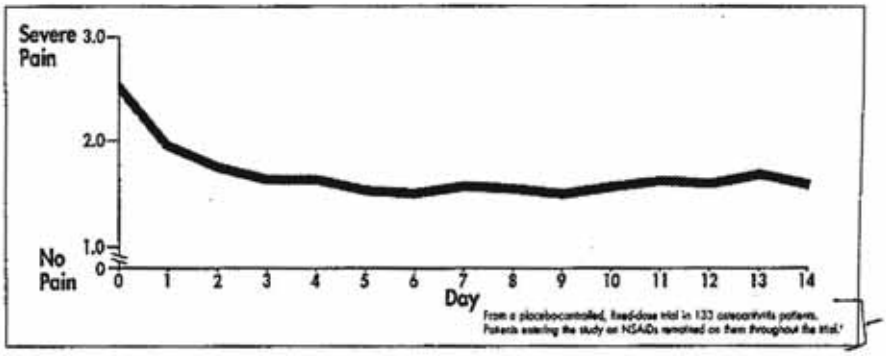
INSERT (A) here

100% of OxyContin patients in clinical trials were dosed q12h

THE ONE TO START WITH.

(A-T-C)

Q12h dosing provides smooth and sustained pain control.



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- Prompt reduction in pain intensity over the first 24 hours
- By Day 3, patients had achieved 94% of their total pain reduction
- Patients reported that OxyContin did not impair their ability to...
  - Sleep
  - Perform normal work
  - Get along with other people
  - Walk
  - Enjoy life

100% of OxyContin patients were dosed q12h

[1]Roth, Burch, Fleischmann, et al. The effect of controlled-release (CR) oxycodone on pain intensity and activities in patients with pain secondary to osteoarthritis. Presented at the American Pain Society, November, 1995, Los Angeles, CA.

larger

New q12h

OXYCONTIN® (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

larger — **Warning**—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

larger — Please see accompanying professional prescribing information.

7

In this study, Oxy Contin 20mg q12h...
- Significantly decreased pain
- Improved quality of life, mood and sleep

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin™ T

Prompt onset of relief:

Analgesic ~~action~~ onset within 1 hour in most patients.

Percent of patients experiencing analgesic onset ~~of pain relief.~~*

larger — From a single-dose study in postoperative patients*

Analgesic onset within 1 hour

— ~~Prompt pain relief~~ plus a longer duration of action than Percocet®, Vicodin®, or Tylenol® with Codeine

larger — *Sunshine PD. Onset, peak, and duration of analgesia using the sorting technique: a comparison of controlled-release oxycodone vs. immediate-release oxycodone alone and in combination with acetaminophen. *American Pain Society Program Book.* 1994; A-36, #94607 (Abstract)

OxyContin clinically studied in various pain syndromes

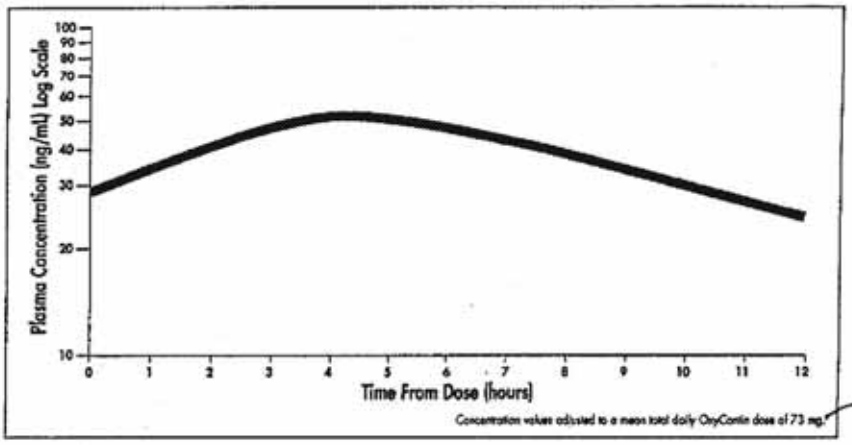
- More than 10 clinical trials
- More than 700 patients with either cancer or noncancer pain
- 100% of patients receiving OxyContin were dosed q12h

THE ONE TO START WITH.

The one to start with (A-T-C)

(A-T-C).

Q12h dosing provides smooth and sustained blood levels.



+] larger

— Fewer "peaks and valleys" than with immediate-release oxycodone

1/M **100% of OxyContin patients were dosed q12h**

larger [+ * Around-the-clock
Data on file, Purdue Pharma L.P.

New q12h

OXYCONTIN™ II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

larger [**Warning**—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

professional

Please see accompanying prescribing information.

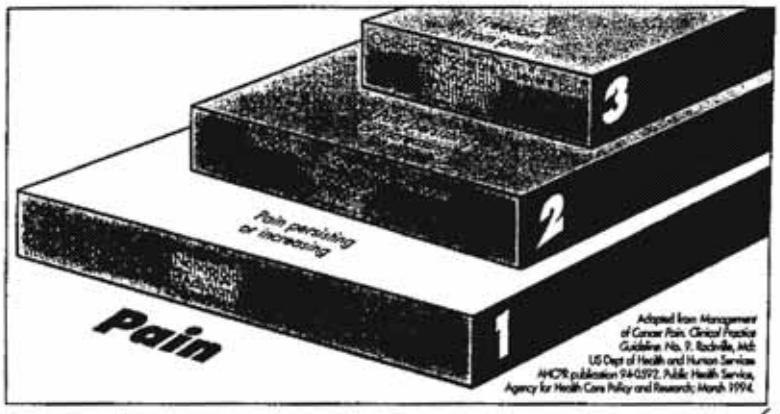
5

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin™

The logical next step for patients with persistent pain no longer responding to or tolerating nonopioids:

Add to or replace nonopioid with OxyContin.



Q12h OxyContin—ideal for initial around-the-clock (A-T-C) opioid therapy.

- Twelve hours of smooth and reliable pain control—less frequent dosing than with short-acting products such as Percocet®, Percodan®, Tylox®, Vicodin®, Lortab®, Lorcet®, and Tylenol® with Codeine

  Oxycodone is the opioid ingredient in Percocet, Percodan, and Tylox
- Patients are spared the added potential toxicities of ~~high~~ maximal daily doses of ASA or APAP
- Convenient q12h schedule won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
- Patients are less likely to anxiously "clock watch" when pain is controlled over long periods

Percodan is a registered trademark of The DuPont Merck Pharmaceutical Co. Tylox is a registered trademark of McNeil Pharmaceutical. Lortab is a registered trademark of Whitby Pharmaceuticals Inc. Lorcet is a registered trademark of UAD Laboratories.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

Introducing New q12h OxyContin™ (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

larger — **Warning**—May be habit forming

The analgesic efficacy of immediate-release oxycodone
The ease of q12h dosing

Twelve hours of smooth and reliable pain control—less frequent dosing than with Percocet®, Vicodin®, or Tylenol® with Codeine

Prompt onset of relief—analgesic action within 1 hour in most patients

Single-entity agent—contains no aspirin or acetaminophen which may be potentially toxic in high daily doses

maximal

No "ceiling" to analgesic efficacy—may be titrated upward when clinically necessary

Common opioid side effects—often diminishing over time for many patients, except for constipation

10mg 20mg 40mg
Small, color-coded tablets (actual size)

larger — **OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioid [illegible] respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.**

↑ including OxyContin

larger — Percocet is a registered trademark of The Du Pont Merck Pharmaceutical Co.
Vicodin is a registered trademark of Knoll Pharmaceutical Company.
Tylenol with Codeine is a registered trademark of McNeil Pharmaceutical.

OxyContin™
The longest-lasting oxycodone ever.

larger — Please see accompanying professional prescribing information.

3

24 Hours Of Oxycodone Pain Control
THE OLD WAY

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

New q12h OxyContin™ CII

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit

The one to start with (A-T-C).*

- The logical "next step" for patients, with persistent pain, no longer tolerating or responding to nonopioids
- Analgesic onset within 1 hour in most patients—pain control lasts 12 hours
- Less frequent dosing than with Percocet®, Vicodin®, or Tylenol® with Codeine

The one to stay with.

- No "ceiling" to analgesic efficacy—may be titrated upward when clinically necessary
- Patients avoid the added risk of gastric/hepatic/renal toxicity that can result from maximal daily doses of ASA or APAP
- Excellent compliance, high degree of patient acceptability during clinical trials

Easy to live with.

- Convenient q12h schedule won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
- Common opioid side effects may be anticipated and effectively managed or prevented; many diminish over time for most patients, except for constipation

Easy to dose.

Actual Size

- Small, color-coded tablets are easy to identify and swallow
- Variety of strengths permit precise titration to an effective dose
- Manage breakthrough or incident pain with IR oxycodone to avoid polypharmacy

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

OxyContin™
The longest-lasting oxycodone ever.

* Around-the-clock.

Please see accompanying professional prescribing information.

A4847 000901 PUR 33040

24 Hours Of Oxycodone Pain Control

THE NEW WAY

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

Introducing New q12h OxyContin™ (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

The analgesic efficacy of immediate-release oxycodone
The ease of q12h dosing

Twelve hours of smooth and reliable pain control—less frequent dosing than with Percocet®, Vicodin®, or Tylenol® with Codeine

Analgesic onset within 1 hour—in most patients

Single-entity agent—contains no aspirin or acetaminophen which may be potentially toxic in maximal daily doses

No "ceiling" to analgesic efficacy—may be titrated upward when clinically necessary

Common opioid side effects—often diminishing over time for many patients, except for constipation

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

Percocet is a registered trademark of The DuPont Merck Pharmaceutical Co. Vicodin is a registered trademark of Knoll Pharmaceutical Company. Tylenol with Codeine is a registered trademark of McNeil Pharmaceutical.

OxyContin™
The longest-lasting oxycodone ever.

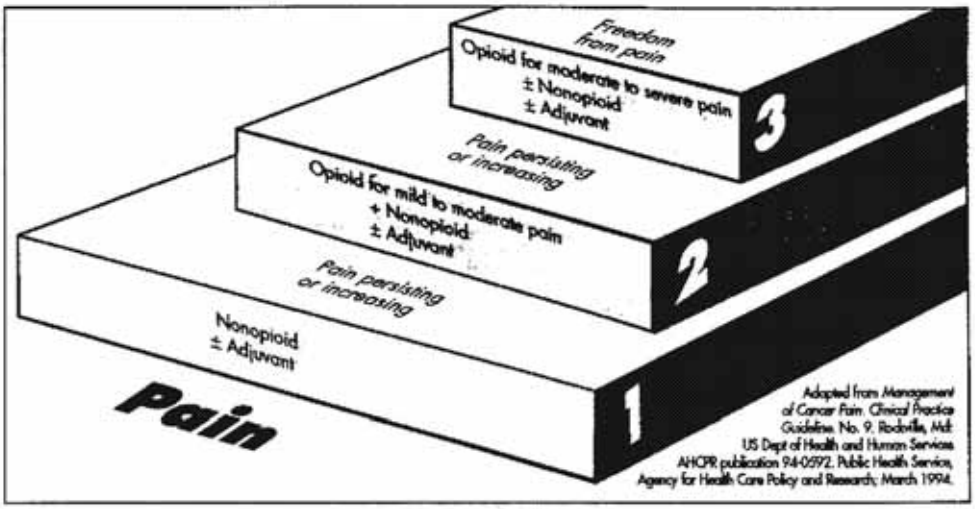
Please see accompanying professional prescribing information.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin

The logical next step for patients, with persistent pain, no longer responding to or tolerating nonopioids:

Add to or replace nonopioid with OxyContin.



Q12h OxyContin—ideal for initial around-the-clock (A-T-C) opioid therapy.

- Twelve hours of smooth and reliable pain control—less frequent dosing than with short-acting products such as Percocet®, Percodan®, Tylox®, Vicodin®, Lortab®, Lorcet®, and Tylenol® with Codeine

  Oxycodone is the opioid ingredient in Percocet, Percodan, and Tylox
- Patients are spared the added potential toxicities of maximal daily doses of ASA or APAP
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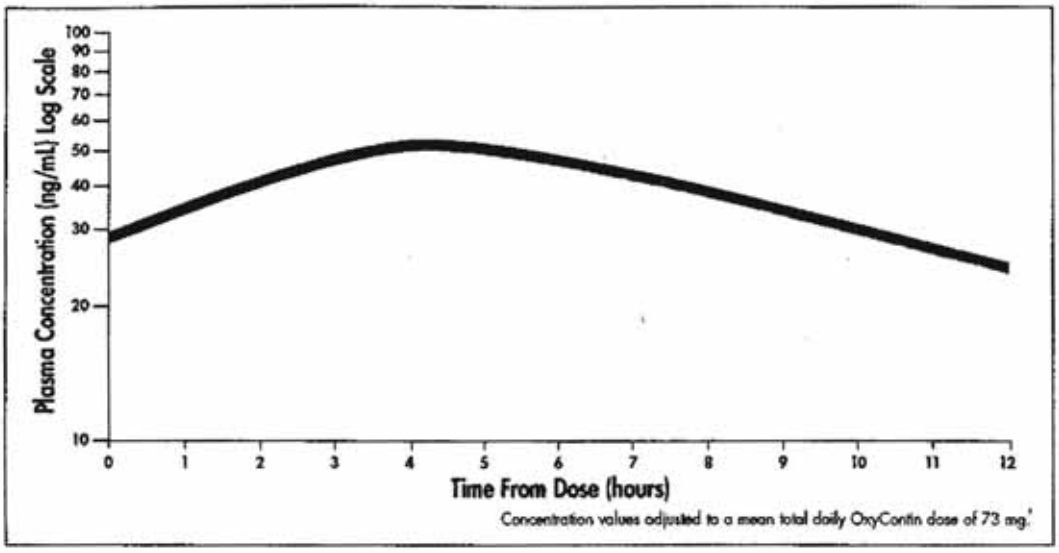
- Patients are less likely to anxiously "clock watch" when pain is controlled over long periods

Percodan is a registered trademark of The DuPont Merck Pharmaceutical Co. Tylox is a registered trademark of McNeil Pharmaceutical. Lortab is a registered trademark of Whitby Pharmaceuticals Inc. Lorcet is a registered trademark of UAD Laboratories.

THE ONE TO START WITH (A-T-C).*

Q12h dosing provides smooth and sustained blood levels.



— 100% of OxyContin patients were dosed q12h

*Around-the-clock.
†Data on file, Purdue Pharma L.P.

New q12h

OXYCONTIN™ (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

Small, color-coded tablets (actual size)

Please see accompanying professional prescribing information.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin

Analgesic onset within 1 hour in most patients.

1 hour

Percent of patients experiencing analgesic onset.

90%

From a single-dose study.*

— Analgesic onset within 1 hour plus a longer duration of action than Percocet®, Vicodin®, or Tylenol® with Codeine

*Sunshine A. Onset, peak, and duration of analgesic effect using the sorting technique: a comparison of controlled-release oxycodone v. immediate release oxycodone alone and in combination with acetaminophen. *American Pain Society Program Book.* 1994; A-36, #94607 (Abstract).

OxyContin clinically studied in various pain syndromes

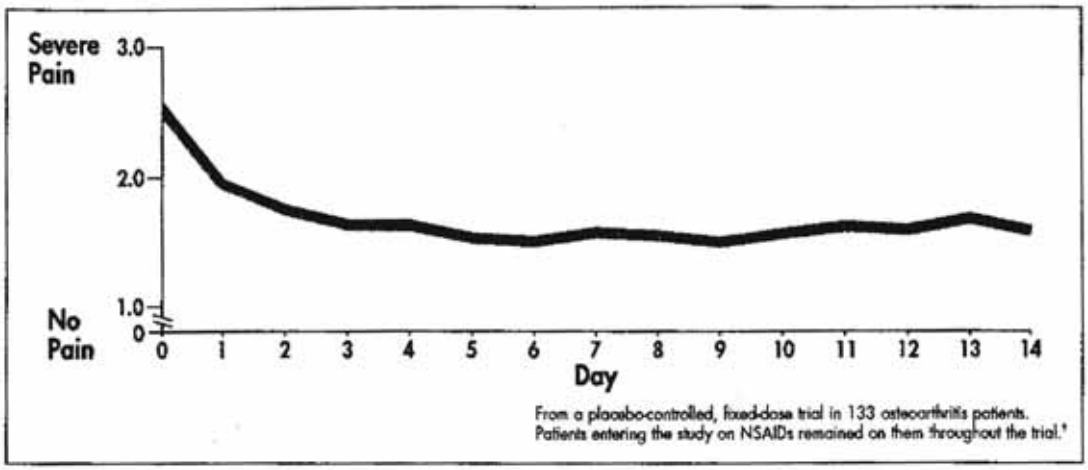
— More than 10 clinical trials

— More than 700 patients with either cancer or noncancer pain

— 100% of patients receiving OxyContin were dosed q12h

THE ONE TO START WITH (A-T-C).

Q12h dosing provides smooth and sustained pain control.



From a placebo-controlled, fixed-dose trial in 133 osteoarthritis patients. Patients entering the study on NSAIDs remained on them throughout the trial.†

- Prompt reduction in pain intensity over the first 24 hours
- By Day 3, patients had achieved 94% of their total pain reduction
- In this study, OxyContin 20mg q12h...
  - Significantly decreased pain
  - Improved quality of life, mood and sleep

100% of OxyContin patients were dosed q12h

†Roth S, Burch F, Fleischmann R, et al. The effect of controlled-release (CR) oxycodone on pain intensity and activities in patients with pain secondary to osteoarthritis. Presented at the American Pain Society, November, 1995, Los Angeles, CA.

New q12h

OXYCONTIN™ (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

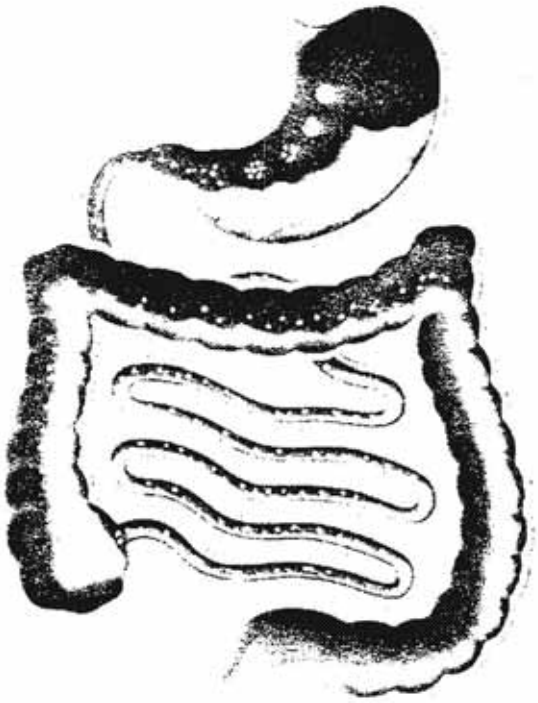
Please see accompanying professional prescribing information.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

The 12-hour

Improved Contin® delivery system allows both rapid and prolonged release.

Rapid release
Analgesic onset within 1 hour as a portion of the active oxycodone is released and absorbed.



Prolonged release
Pain control continues as tablet matrix slowly releases the remainder of the oxycodone.

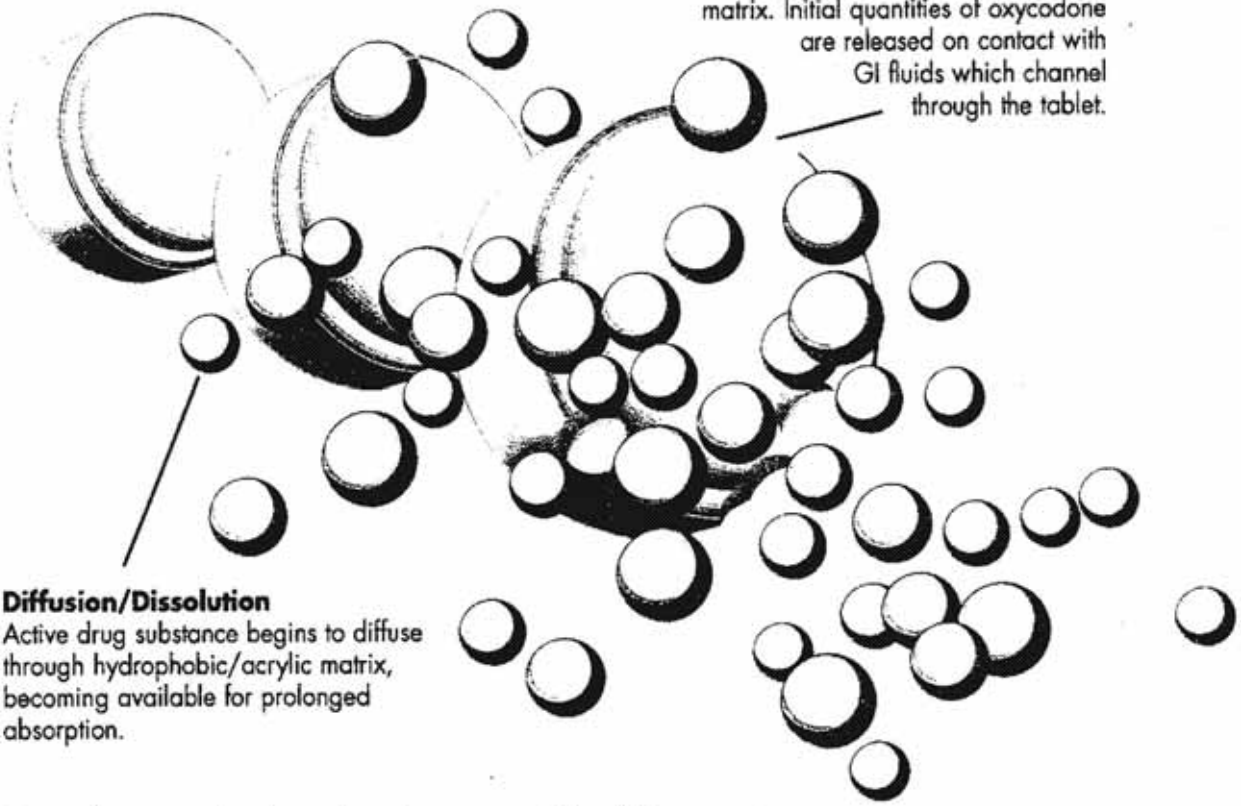
"pH independence" assures...
Minimal effect of stomach contents on absorption—bioavailability unaffected by food.

100% of OxyContin patients in clinical trials were dosed q12h

ACROCONTIN Delivery System.

The OxyContin™ CII (oxycodone HCl controlled-release) Tablets Dual Action Delivery System.

Dissolution
Gastrointestinal fluids dissolve tablet surface, exposing hydrophobic/acrylic matrix. Initial quantities of oxycodone are released on contact with GI fluids which channel through the tablet.



Diffusion/Dissolution
Active drug substance begins to diffuse through hydrophobic/acrylic matrix, becoming available for prolonged absorption.

Special patented polymer/acrylic matrix of the delivery system renders OxyContin Tablets "pH independent," allowing uniform release within an acid environment (the stomach) or an alkaline environment (the intestines).

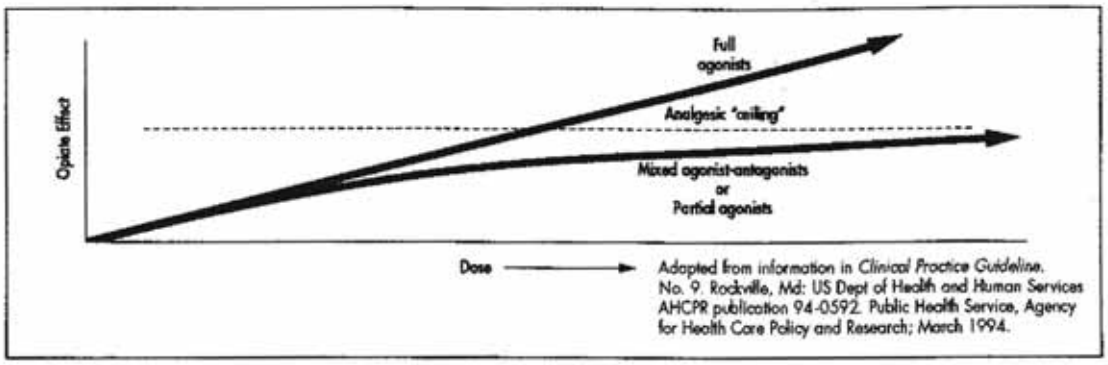
OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.

Please see accompanying professional prescribing information.

For patients with moderate to severe pain requiring opioid therapy for more than a few days

OxyContin

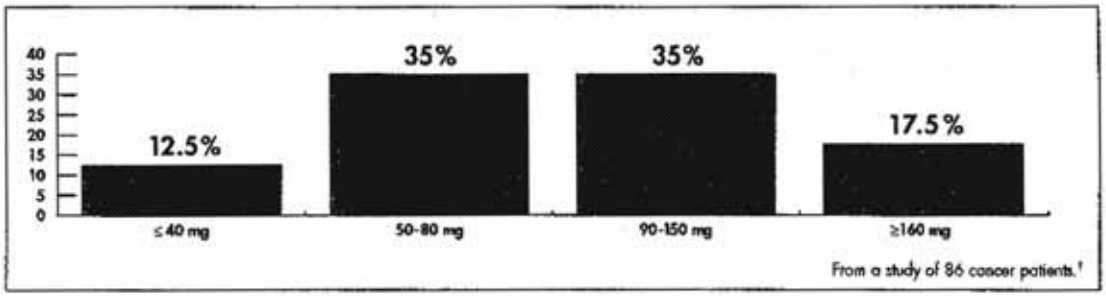
No ceiling to analgesic efficacy.



— With full agonists, such as oxycodone, "effectiveness with increasing doses is not limited by a 'ceiling'."*

OxyContin may be dosed upward as clinically necessary.

Percent of cancer patients receiving various daily doses of OxyContin at the end of a 12-week trial.



Ideal for long-term opioid therapy

— A single-entity oral agent—contains no APAP or ASA; allows independent coadministration and dosage adjustments with nonopioid of choice

THE ONE TO STAY WITH.

A single-entity agent—dose not limited by ASA or APAP "ceilings."

Product (opioid/nonopioid ratio [mg])	Nonopioid Ingredient	Maximum Recommended Daily Dose of Nonopioid Ingredient: Goodman & Gilman‡	Maximum Recommended Daily Dose of Nonopioid Ingredient: Regimen Should Not Exceed...
OxyContin™	**N/A**	**N/A**	**N/A**
Percocet® (5/325)	APAP	4 G	12 tabs/day
Percodan® (5/325)	ASA	6 G	18 tabs/day
Tylox® (5/500)	APAP	4 G	8 tabs/day
Vicodin® (5/500)	APAP	4 G	8 tabs/day†
Vicodin® ES (7.5/750)	APAP	4 G	5 tabs/day†
Lorcet®-HD (5/500)	APAP	4 G	8 tabs/day
Lorcet® (10/650)	APAP	4 G	6 tabs/day†
Lortab® (2.5/500)	APAP	4 G	8 tabs/day†
Lortab® (5/500)	APAP	4 G	8 tabs/day†
Lortab® (7.5/500)	APAP	4 G	6 tabs/day†
Lortab® ASA (5/500)	ASA	6 G	8 tabs/day†
Tylenol® with Codeine			
No. 2 (15/300)	APAP	4 G	13 tabs/day†
No. 3 (30/300)	APAP	4 G	12 tabs/day†
No. 4 (60/300)	APAP	4 G	6 tabs/day†

* *Management of Cancer Pain: Adults. Clinical Practice Guideline.* Quick Reference Guide for Clinicians. Rockville, Md: US Dept of Health and Human Services AHCPR publication 94-0593. Public Health Service, Agency for Health Care Policy and Research; March 1994.

†Kaplan R, Parris W, Croghan M, et al. Decrease in opioid-related adverse experiences (AE) during chronic therapy with controlled-release oxycodone (OxyCR) in cancer pain patients. Presented at the American Pain Society, November, 1995, Los Angeles, CA.

‡Insel PA. Analgesic-antipyretics and anti-inflammatory agents; drugs employed in the treatment of rheumatoid arthritis and gout. In: Goodman LS, Gilman A, eds. *The Pharmacological Basis of Therapeutics.* New York, NY: McGraw-Hill, Inc.; 1990:638-681.

†*Physicians' Desk Reference®.* 49th ed. Montvale, NJ: Medical Economics Data; 1995:(see respective product names).

New q12h

OxyContin™ II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

Please see accompanying professional prescribing information.

11

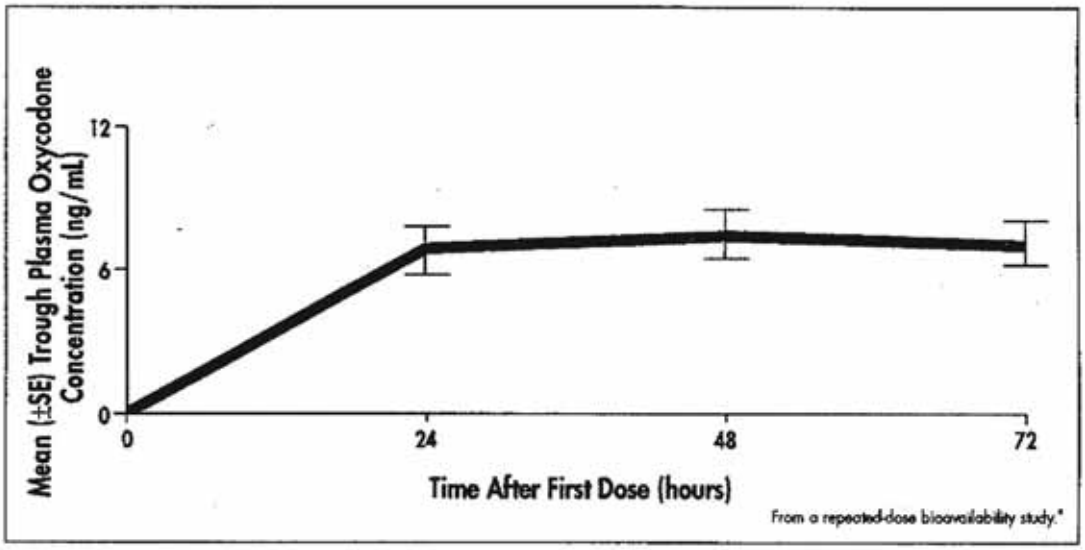
The one to stay with

For patients with moderate to severe pain requiring opioid therapy for more than a few days

OxyContin®

Easy to titrate:

Steady-state blood levels achieved in 24-36 hours.



— If needed, pain assessment and titration may be carried out every 1 to 2 days—especially important for patients with rapidly escalating pain

*Reder R, Kaiko R, Grandy R, et al. Steady-state bioavailability comparison of controlled release oxycodone (OxyContin) tablets vs. oxycodone oral liquid. *American Pain Society Program*. 1994; A-36, #94604 (Abstract).

THE ON[illegible] STAY WITH

In cancer studies†...

- Titration enhanced efficacy of therapy—only 3.5% of cancer patients discontinued (due to inadequate pain control) when allowed to titrate and use rescue medication
- Patients were titrated as quickly and easily with OxyContin as with immediate-release oxycodone
- 92% of patients were titrated to stable pain control with OxyContin
- Average time to stable pain control was 2 days

† Data on file, Purdue Pharma L.P.

100% of OxyContin patients were dosed q12h

easy to titrate

New q12h

OXYCONTIN™ II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

Please see accompanying professional prescribing information.

13

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin™

Common opioid side effects; many diminish over time, except for constipation.

Adverse experiences reported over time by cancer patients (n=86)*

Drug-related ADE	Week 1 (%)^	Week 5 (%)^	Week 10 (%)^
Nausea	20	12	4
Sedation	14	8	8
Dry Mouth	9	0	0
Vomiting	8	7	0
Pruritus	7	0	0
Dizziness	5	5	0

^ Percent of patients reporting ADE once or more during specified week of OxyContin therapy.

- The most serious risk associated with opioids is respiratory depression
- A significant decrease in the percent of patients reporting adverse events was seen between the first and last weeks of the study ($P<0.0001$)
- Most side effects diminished over time, except for constipation, even as daily doses increased
- Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness

* Kaplan R, Parris W, Croghan M, et al. Decrease in opioid-related adverse experiences (AE) during chronic therapy with controlled-release oxycodone (OxyCR) in cancer pain patients. Presented at the American Pain Society, November, 1995, Los Angeles, CA.

EASY TO LIVE WITH.

The AHCPR, in *Management of Cancer Pain*, recommends that side effects be treated aggressively...

"**Constipation** is a common problem associated with opioid administration. (It) can usually be managed by an increase in fiber consumption and the use of a mild laxative...." If more severe, it can be treated with a "stimulating cathartic drug, e.g.,...senna concentrate."

"Transitory **sedation** is common when opioid doses are increased substantially, but tolerance usually develops rapidly."

Nausea and vomiting. "As with other side effects, it is important to determine the cause. Clinical experience suggests that opioid-induced nausea and vomiting can be managed with antiemetics chosen according to their modes of action."

From *Management of Cancer Pain. Clinical Practice Guideline.* No. 9. Rockville, Md: US Dept of Health and Human Services AHCPR publication 94-0592. Public Health Service, Agency for Health Care Policy and Research; March 1994.

New q12h

OXYCONTIN™ (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

Please see accompanying professional prescribing information.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin®

Starting on OxyContin.

Recommended initial dose for opioid-naive patients.

For around-the-clock pain:

OxyContin™ CII

10 mg q12h

If a nonopioid analgesic is being taken, it may be continued.

Warning: Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. See WARNINGS and PRECAUTIONS Sections in professional prescribing information.

For supplemental analgesia:

Immediate-Release (IR) Oxycodone*

5 mg administered 1 hour before anticipated incident pain

5 mg administered for breakthrough pain (if needed)

Note: If more than two rescue doses are needed per day, OxyContin should be titrated upward.

Converting to OxyContin.

Fixed-Combination Opioid/ Nonopioid Products ⟶ **OxyContin**

Dose of regular-strength products (eg, Percocet®, Percodan®, Tylox®, Vicodin®, Lortab®, Lorcet®, or Tylenol® with Codeine)	Recommended OxyContin conversion dose range	IR oxycodone rescue dose for breakthrough pain*
1-5 Tablets/Capsules/ Caplets per day	10-20 mg q12h	5 mg
6-9 Tablets/Capsules/ Caplets per day	20-30 mg q12h	5-10 mg
10-12 Tablets/Capsules/ Caplets per day	30-40 mg q12h	10 mg

Note: The nonopioid ingredient may be continued as a separate drug. Discontinue all other around-the-clock opioids when initiating OxyContin therapy.

*See professional prescribing information for immediate-release oxycodone.

EASY TO DOSE.

The goal of titration:

To effectively control pain with two or fewer rescue doses per day.

OxyContin Titration Guide

	OxyContin Tablets q12h dose	IR oxycodone dose for rescue*	
10 mg	10 mg q12h	5 mg	Titrate the OxyContin dose if more than two rescue doses per day are needed.
	20 mg q12h	5 mg	
	30 mg q12h	10 mg	
20 mg	40 mg q12h	10 mg	
	60 mg q12h	15 mg	
40 mg	80 mg q12h	20 mg	
	120 mg q12h	30 mg	
	Continue titrating, if necessary, using the T•I•M•E principles below.		

Titrate patients every 1-2 days, if necessary.

Increase the dose by 25%-50%, if necessary†; do not increase the dosing frequency.

Manage breakthrough pain with IR oxycodone* at ¼ to ⅓ of the 12-hour OxyContin dose.†

Elevate the OxyContin dose if more than two rescue doses are required per day.

†For patients taking OxyContin 10 mg q12h...

- The next titration step should be 20 mg q12h
- Breakthrough pain should be managed with IR oxycodone 5 mg

New q12h

OXYCONTIN™ II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

Please see accompanying professional prescribing information.

Easy to dose

OxyContin™ 10 mg Tablets
OxyContin™ 20 mg Tablets
OxyContin™ 40 mg Tablets

CII

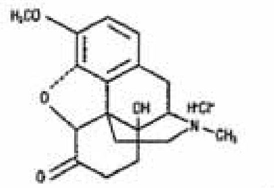
(Oxycodone Hydrochloride Controlled-Release)

WARNING: May Be Habit Forming

A4908-011

DESCRIPTION

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are an opioid analgesic supplied in 10 mg, 20 mg, and 40 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The chemical formula is 4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio-methacrylate copolymer, hydroxypropyl methylcellulose, lactose, magnesium stearate, povidone, red iron oxide (20 mg strength tablet only), stearyl alcohol, talc, titanium dioxide, triacetin, yellow iron oxide (40 mg strength tablet only), and other ingredients.

CLINICAL PHARMACOLOGY

Central Nervous System

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria and feelings of relaxation. Like all pure opioid agonists, there is no ceiling effect to analgesia, such as is seen with partial agonists or non-opioid analgesics.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic. Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration—Efficacy Relationships (Pharmacodynamics)

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects. In normal volunteers these include pupillary constriction, sedation and overall "drug effect" and in patients, analgesia and feelings of "relaxation." In non-tolerant patients, analgesia is not usually seen at a plasma oxycodone concentration of less than 5–10 ng/mL.

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase with repeated dosing due to an increase in pain and/or the development of tolerance.

Concentration—Adverse Experience Relationships

OxyContin™ tablets are associated with typical opioid-related adverse experiences similar to those seen with immediate-release oxycodone and all opioids. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is poorly understood.

As with all opioids, the dose must be individualized (see DOSAGE AND ADMINISTRATION), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

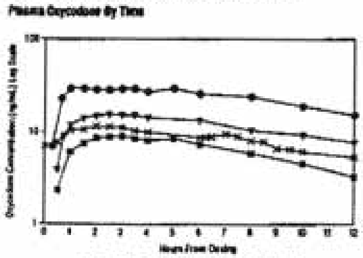
PHARMACOKINETICS AND METABOLISM

The activity of OxyContin™ (oxycodone hydrochloride controlled-release) tablets is primarily due to the parent drug oxycodone. OxyContin tablets are designed to provide controlled delivery of oxycodone over 12 hours. Oxycodone is well absorbed from OxyContin tablets with an oral bioavailability of from 60% to 87%. The relative oral bioavailability of OxyContin to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers, steady-state levels were achieved within 24-36 hours. Dose proportionality has been established for the 10 mg, 20 mg and 40 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers the $t_{1/2}$ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone By Time



Dose proportionality has been established for the 10 mg, 20 mg and 40 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Given the short half-life of elimination of oxycodone from OxyContin, steady-state plasma concentrations of oxycodone are achieved within 24–36 hours of initiation of dosing with OxyContin tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours the two treatments were found to be equivalent for AUC and C_{max} and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin tablets than for the immediate-release formulation.

Table 1

Mean [% coefficient variation]

Regimen/ Dosage Form	AUC (ng·hr/mL)†	C_{max} (ng/mL)	T_{max} (hr)	Trough Conc. (ng/mL)
Single Dose				
10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
Multiple Dose 10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

†for single-dose AUC = AUC_{0-inf}; for multiple-dose AUC = AUC_{0-T}

Food Effects

In contrast to immediate-release formulations, food has no significant effect on the absorption of oxycodone from OxyContin. Oxycodone release from OxyContin tablets is pH independent.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen and brain. Oxycodone has been found in breast milk (see PRECAUTIONS).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known at present.

The formation of oxymorphone, but not noroxycodone, is mediated by CYP2D6 and as such its formation can, in theory, be affected by other drugs (see Drug-Drug Interactions).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects. There were no differences in adverse event reporting between young and elderly subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Preliminary data from a study involving patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone 60%, 50% and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour (see PRECAUTIONS).

Hepatic Impairment

Preliminary data from a study involving patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours (see PRECAUTIONS).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part via CYP2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination can be blocked by a variety of drugs (e.g., certain cardiovascular drugs and anti-depressants). Patients receiving such drugs concomitantly with OxyContin do not appear to present different therapeutic profiles than other patients.

CLINICAL TRIALS

OxyContin™ (oxycodone hydrochloride controlled-release) tablets were evaluated in studies involving 713 patients with either cancer or non-cancer pain. All patients receiving OxyContin were dosed q12h. Efficacy comparable to other forms of oral oxycodone was demonstrated in clinical studies using pharmacokinetic, pharmacodynamic and efficacy outcomes. The outcome of these trials indicated: (1) a positive relationship between dose and plasma oxycodone concentration, (2) a positive relationship between plasma oxycodone concentration and analgesia, and (3) an observed peak to trough variation in plasma concentration with OxyContin lying within the observed range established with qid dosing of immediate-release oxycodone in clinical populations at the same total daily dose.

In clinical trials, OxyContin tablets were substituted for a wide variety of analgesics, including acetaminophen (APAP), aspirin (ASA), other non-steroidal anti-inflammatory drugs (NSAIDs), opioid combination products and single-entity opioids, primarily morphine. In cancer patients receiving adequate opioid therapy at baseline, pain intensity scores and acceptability of therapy remained unchanged by transfer to OxyContin. For non-cancer pain patients who had moderate to severe pain at baseline on prn opioid therapy, pain control and acceptability of therapy improved with the introduction of fixed-interval therapy with OxyContin.

Use in Cancer Pain

OxyContin was studied in three double-blind, controlled clinical trials involving 341 cancer patients and several open-label trials with therapy durations of over 10 months.

Two, double-blind, controlled clinical studies indicated that OxyContin dosed q12h produced analgesic efficacy equivalent to immediate-release oxycodone dosed qid at the same total daily dose. Peak and trough plasma concentrations attained were similar to those attained with immediate-release oxycodone at equivalent total daily doses. With titration to analgesic effect and proper use of rescue medication, nearly every patient achieved adequate pain control with OxyContin.

In the third study, a double-blind, active-controlled, crossover trial, OxyContin dosed q12h was shown to be equivalent in efficacy and safety to immediate-release oxycodone dosed qid at the same total daily dose. Patients were able to be titrated to an acceptable analgesic effect with either OxyContin or immediate-release oxycodone with both treatments providing stable pain control within 2 days in most patients.

In patients with cancer pain, the total daily OxyContin doses tested ranged from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Studies in Non-Cancer Pain

A double-blind, placebo-controlled, fixed-dose, parallel group study was conducted in 133 patients with moderate to severe osteoarthritis pain, who were judged as having inadequate pain control with prn opioids and maximal non-steroidal anti-inflammatory therapy. In this study, 20 mg OxyContin q12h significantly decreased pain and improved quality of life, mood and sleep, relative to placebo. Both dose-concentration and concentration-effect relationships were noted with a minimum effective plasma oxycodone concentration of approximately 5–10 ng/mL.

In a double-blind, active-controlled, crossover study involving 57 patients with low-back pain inadequately controlled with prn opioids and non-opioid therapy, OxyContin administered q12h provided analgesia equivalent to immediate-release oxycodone administered qid. Patients could be titrated to an acceptable analgesic effect with either OxyContin or immediate-release forms of oxycodone.

Single-Dose Comparison with Standard Therapy

A single-dose, double-blind, placebo-controlled, post-operative study of 182 patients was conducted utilizing graded doses of OxyContin (10, 20 and 30 mg). Twenty and 30 mg of OxyContin gave equivalent peak analgesic effect compared to two oxycodone 5 mg /acetaminophen 325 mg tablets and to 15 mg immediate-release oxycodone, while the 10 mg dose of OxyContin was intermediate between both the immediate-release and combination products and placebo. The onset of analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery) because the safety or appropriateness of fixed-dose, long-acting opioids in this setting has not been established.

Other Clinical Trials

In open-label trials involving approximately 200 patients with cancer-related and non-cancer pain, dosed according to the package insert recommendations, appropriate analgesic effectiveness was noted without regard to age, gender, race, or disease state. There were no unusual drug interactions observed in patients receiving a wide range of medications common in these populations.

For opioid-naive patients, the average total daily dose of OxyContin was approximately 40 mg per day. There was no evidence of oxycodone and metabolite accumulation during 8 months of therapy. For cancer pain patients the average total daily dose was 105 mg (range 20 to 720 mg) per day. There was a significant decrease in acute opioid-related side effects, except for constipation, during the first several weeks of therapy. Development of significant tolerance to analgesia was uncommon.

INDICATIONS AND USAGE

OxyContin™ tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. (See: CLINICAL PHARMACOLOGY; CLINICAL TRIALS).

CONTRAINDICATIONS

OxyContin™ is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OxyContin™ (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODONE.

Respiratory Depression

Respiratory depression is the chief hazard from all opioid agonist preparations. Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin™, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. OxyContin may produce orthostatic hypotension in ambulatory patients. OxyContin, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are intended for use in patients who require oral pain therapy with an opioid agonist of more than a few days duration. As with any opioid analgesic, it is critical to adjust the dosing regimen individually for each patient (see DOSAGE AND ADMINISTRATION).

Selection of patients for treatment with OxyContin should be governed by the same principles that apply to the use of similar controlled-release opioid analgesics (see INDICATIONS AND USAGE). Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension. Physicians should individualize treatment in every case, using non-opioid analgesics, prn opioids and/or combination products, and chronic opioid therapy with drugs such as OxyContin in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Care Policy and Research, and the American Pain Society.

Use of OxyContin is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin, like all opioid analgesics, should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Patients who are already receiving OxyContin tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given and the temporary changes in physiology caused by the surgical intervention (see PRECAUTIONS: Drug-Drug Interactions, and DOSAGE AND ADMINISTRATION).

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

Significant tolerance should not occur in most of the patients treated with the lowest doses of oxycodone. It should be expected, however, that a fraction of cancer patients will develop some degree of tolerance and require progressively higher dosages of OxyContin to maintain pain control during chronic treatment. Regardless of whether this occurs as a result of increased pain secondary to disease progression or pharmacological tolerance, dosages can usually be increased safely by adjusting the patient's dose to maintain an acceptable balance between pain relief and side effects. The dosage should be selected according to the patient's individual analgesic response and ability to tolerate side effects. Tolerance to the analgesic effect of opioids is usually paralleled by tolerance to side effects, except for constipation.

Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity (see OVERDOSAGE). If OxyContin is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. This is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate or heart rate.

If signs and symptoms of withdrawal occur, patients should be treated by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of OxyContin combined with symptomatic support (see DOSAGE AND ADMINISTRATION: Cessation of Therapy).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin (oxycodone hydrochloride controlled-release) tablets or their caregivers should be given the following information by the physician, nurse, pharmacist or caregiver:

1. Patients should be advised that OxyContin tablets were designed to work properly only if swallowed whole. They may release all their contents at once if broken, chewed or crushed, resulting in a risk of overdose.
2. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
3. Patients should be advised not to adjust the dose of OxyContin without consulting the prescribing professional.

4. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
5. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur.
6. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
7. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
8. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
9. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs which cause central nervous system depression.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at ⅓ to ½ of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers and alcohol because respiratory depression, hypotension and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Mutagenicity

Studies of oxycodone in animals to evaluate its carcinogenic and mutagenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Pregnancy

Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg (48 mg/m²) and 125 mg/kg (1375 mg/m²), respectively. These doses are 4 and 60 times a human dose of 120 mg/day (74 mg/m²), based on mg/kg of a 60 kg adult (0.7 and 19 times this human dose based upon mg/m²). The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects—Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Labor and Delivery

OxyContin is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin since oxycodone may be excreted in the milk.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established with this dosage form of oxycodone. However, oxycodone has been used extensively in the pediatric population in other dosage forms, as have the excipients used in this formulation. No specific increased risk is expected from the use of this form of oxycodone in pediatric patients old enough to safely take tablets if dosing is adjusted for the patient's weight (see DOSAGE AND ADMINISTRATION). **It must be remembered that OxyContin tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15%. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen based on age, and the usual doses and dosing intervals are appropriate for the geriatric patient. As with all opioids, the starting dose should be reduced to ⅓ to ½ of the usual dosage in debilitated, non-tolerant patients.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at ⅓ to ½ the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

Serious adverse reactions which may be associated with OxyContin™ (oxycodone hydrochloride controlled-release) tablet therapy in clinical use are those observed with other opioid analgesics, including: respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension or shock (see OVERDOSE).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

In clinical trials comparing OxyContin with immediate-release oxycodone and placebo, the most common adverse events (> 5%) reported by patients (pts) at least once during therapy were:

Table 2

	OxyContin n=227 # pts (%)		Immediate-Release n=225 # pts (%)		Placebo n=45 # pts (%)	
Constipation	52	(23)	58	(26)	3	(7)
Nausea	52	(23)	60	(27)	5	(11)
Somnolence	52	(23)	55	(24)	2	(4)
Dizziness	29	(13)	35	(16)	4	(9)
Pruritus	29	(13)	28	(12)	1	(2)
Vomiting	27	(12)	31	(14)	3	(7)
Headache	17	(7)	19	(8)	3	(7)
Dry Mouth	13	(6)	15	(7)	1	(2)
Asthenia	13	(6)	15	(7)	—	—
Sweating	12	(5)	13	(6)	1	(2)

The following adverse experiences were reported in OxyContin treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials:

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, peripheral edema, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypokinesia, malaise, paresthesia, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis

Special Senses: abnormal vision, taste perversion

Urogenital: dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

DRUG ABUSE AND DEPENDENCE (Addiction)

OxyContin™ is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Iatrogenic "addiction" to opioids legitimately used in the management of pain is very rare. "Drug seeking" behavior is very common to addicts. Tolerance and physical dependence in pain patients are *not* signs of psychological dependence. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Most chronic pain patients limit their intake of opioids to achieve a balance between the benefits of the drug and dose-limiting side effects.

Physicians should be aware that psychological dependence may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true psychological dependence and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin consists of a dual-polymer matrix, intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OxyContin™. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OxyContin™ (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODONE.

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin is intended for the management of moderate to severe pain in patients who require treatment with an oral opioid analgesic for more than a few days. The controlled-release nature of the formulation allows it to be effectively administered every 12 hours. (See CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM.) While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient
(2) the daily dose, potency and kind of the analgesic(s) the patient has been taking
(3) the reliability of the conversion estimate used to calculate the dose of oxycodone
(4) the patient's opioid exposure and opioid tolerance (if any)
(5) the balance between pain control and adverse experiences

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see PRECAUTIONS: Drug-Drug Interactions).

Patients Not Already Taking Opioids (opioid naive)

Clinical trials have shown that patients may initiate analgesic therapy with OxyContin. A reasonable starting dose for most patients who are opioid naive is 10 mg q12h. If a non-opioid analgesic [(aspirin (ASA), acetaminophen (APAP) or a non-steroidal anti-inflammatory (NSAID)] is being provided, it may be continued. If the current non-opioid is discontinued, early upward dose titration may be necessary.

Conversion from Fixed-Ratio Opioid/APAP, ASA, or NSAID Combination Drugs

Patients who are taking 1 to 5 tablets/capsules/caplets per day of a regular strength fixed-combination opioid/non-opioid should be started on 10 to 20 mg OxyContin q12h. For patients taking 6 to 9 tablets/capsules/ caplets, a starting dose of 20 to 30 mg q12h is suggested. For those taking 10 to 12 tablets, caplets or capsules a day, 30 to 40 mg q12h should be considered. The non-opioid may be continued as a separate drug. Alternatively, a different non-opioid analgesic may be selected. If the decision is made to discontinue the non-opioid analgesic, consideration should be given to early upward titration.

Patients Currently on Opioid Therapy

If a patient has been receiving opioid-containing medications prior to OxyContin therapy, the total daily (24-hour) dose of the other opioids should be determined.

1. Using standard conversion ratio estimates (see Table 3 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. Divide this 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.
3. Round down to a dose which is appropriate for the tablet strengths available (10, 20, and 40 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.

No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 3 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 3

*Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone**

(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codeine	0.15	—
Fentanyl TTS	SEE BELOW	SEE BELOW
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

*To be used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of immediate-release oral oxycodone or another suitable short-acting analgesic.

OxyContin can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see PRECAUTIONS).

Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 µg/hr fentanyl transdermal patch. The patient should be followed closely for early titration as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyContin may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Rescue medication should be available (see: Supplemental Analgesia). Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the health-care team, the patient and the caregiver/family.

Supplemental Analgesia

Most cancer patients given around-the-clock therapy with controlled-release opioids will need to have immediate-release medication available for "rescue" from breakthrough pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Rescue medication can be immediate-release oxycodone, either alone or in combination with acetaminophen, aspirin or other NSAIDs as a supplemental analgesic. The supplemental analgesic should be prescribed at ⅛ to ¼ of the 12-hour OxyContin dose as shown in Table 4. The rescue medication is dosed as needed for breakthrough pain and administered one hour before anticipated incident pain. If more than two doses of rescue medication are needed within 24 hours, the dose of OxyContin should be titrated upward. Caregivers and patients using prn rescue analgesia (a combination with around-the-clock opioids should be advised to report incidents of breakthrough pain to the physician managing the patient's analgesia (see Information for Patients/Caregivers).

Table 4

Table of Appropriate Supplemental Analgesia

OxyContin q12h Dose (mg)	prn Rescue Dose Immediate-release oxycodone (mg)
10 (1×10 mg)	5
20 (2×10 mg)	5
30 (3×10 mg)	10
40 (2×20 mg)	10
60 (3×20 mg)	15
80 (2×40 mg)	20
120 (3×40 mg)	30

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with OxyContin tablets, patients receiving doses of 20–60 mg/day can usually have the therapy stopped abruptly without incident. However, higher doses should be tapered over several days to prevent signs and symptoms of withdrawal in the physically dependent patient. The daily dose should be reduced by approximately 50% for the first two days and then reduced by 25% every two days thereafter until the total dose reaches the dose recommended for opioid naive patients (10 or 20 mg q12h). Therapy can then be discontinued.

If signs of withdrawal appear, tapering should be stopped. The dose should be slightly increased until the signs and symptoms of opioid withdrawal disappear. Tapering should then begin again but with longer periods of time between each dose reduction.

Conversion from OxyContin to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed. Initiate treatment with about 50% of the estimated equianalgesic daily dose of parenteral opioid divided into suitable individual doses based on the appropriate dosing interval, and titrate based upon the patient's response.

SAFETY AND HANDLING

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

HOW SUPPLIED

OxyContin™ (oxycodone hydrochloride controlled-release) 10 mg tablets are round, unscored, white-colored, convex tablets bearing the symbol OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100

OxyContin (oxycodone hydrochloride controlled-release) 20 mg tablets are round, unscored, pink-colored, convex tablets bearing the symbol OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100

OxyContin (oxycodone hydrochloride controlled-release) 40 mg tablets are round, unscored, yellow-colored, convex tablets bearing the symbol OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100

Store tablets at controlled room temperature 15–30°C (59–86°F).

Dispense in tight, light-resistant container.

CAUTION

DEA Order Form Required.

Federal law prohibits dispensing without prescription.

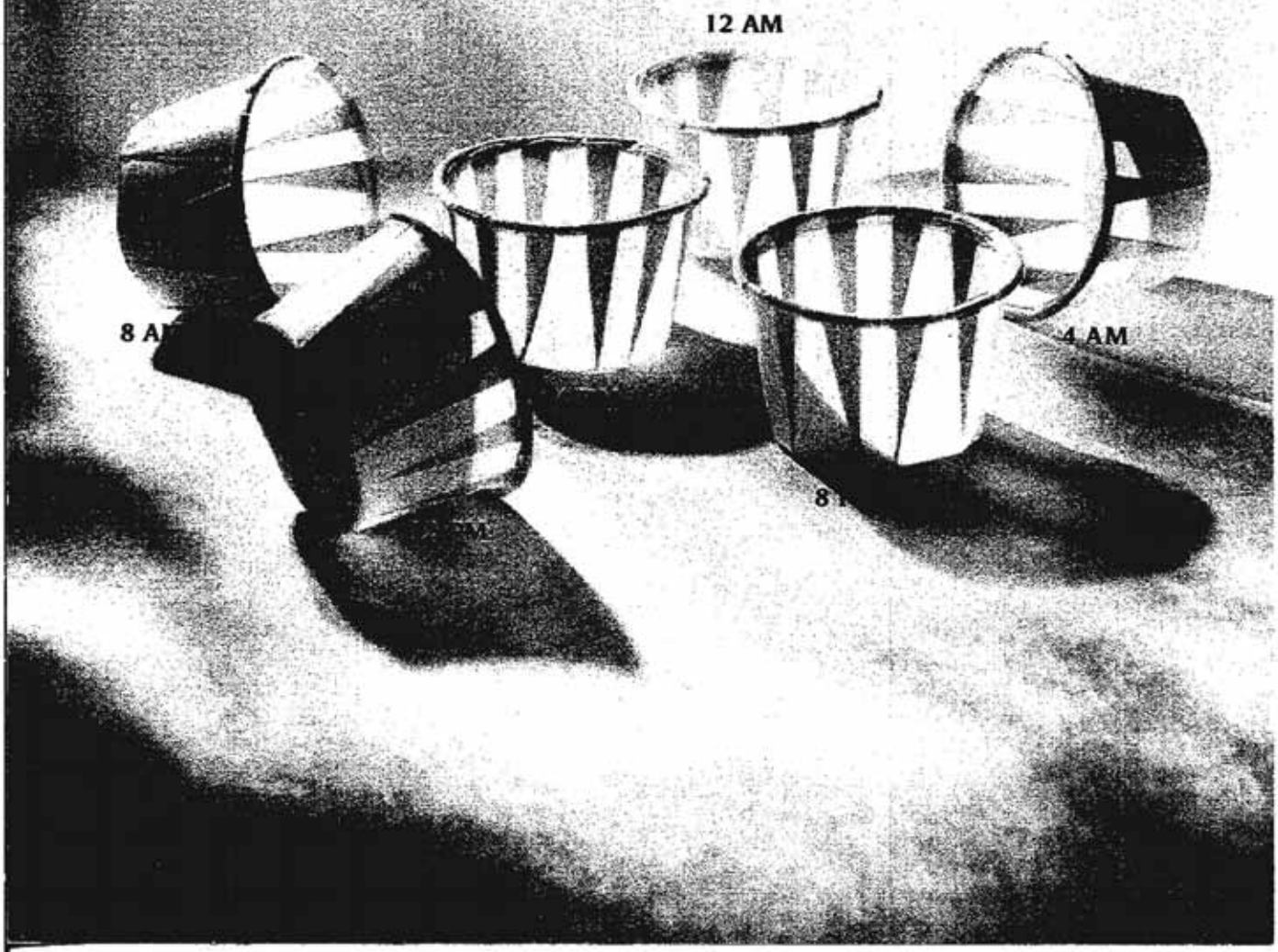
Manufactured by The PF Laboratories, Inc.
Totowa, N.J. 07512

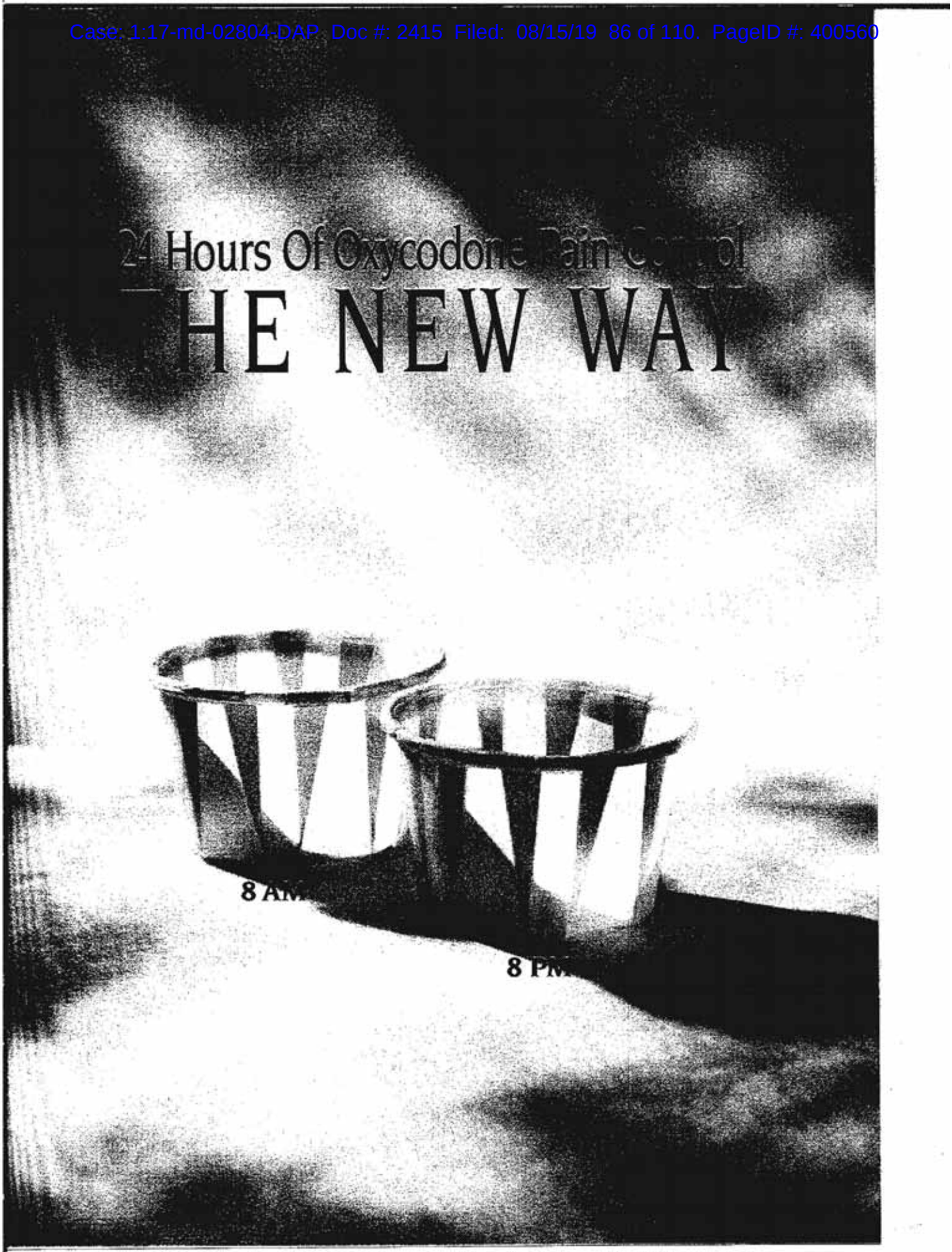
Distributed by Purdue Pharma L.P.
Norwalk, CT 06850-3590

U.S. Patent Numbers 4,861,598; 4,970,075; and 5,266,331

December 5, 1995
A4909-811

24 Hours Of Oxycodone Pain Control
THE OLD WAY




24 Hours Of Oxycodone Pain Control
THE NEW WAY
8 AM
8 PM

INTRODUCING

New q12h

OxyContin® CII

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

10mg 20mg 40mg

The first and only q12h oxycodone.

Brought to you by the makers of MS Contin® Tablets CII (morphine sulfate controlled-release).

Heavy promotional support planned.

— Promoted by over 300 dedicated professionals—the same sales force that boosted sales of MS Contin® to over $100 million.*

— Journal advertising and direct mail to doctors, nurses, pharmacists, hospitals, hospices, and managed care organizations.

Wholesaler/Chain Introductory Offer

Extended Dating: 60 days' extended dating* (total 90 days)

Promotional Period: January 1, 1996–March 29, 1996

First Ship Date: January 2, 1996

Retailers can earn a stocking rebate directly from Purdue Pharma based on their initial order of OxyContin purchased from January 1, 1996 to March 29, 1996.

Order your initial supply of OxyContin Tablets now! Orders must be accompanied by a DEA 222-C form; no phone orders accepted.

*Please submit your order on a separate DEA 222-C form to receive extended dating.

*12-month sales through October 1995. *IMS Drug Store and Hospital Audit*, October 1995.

Promotional Ad Slick

Now Available Through

Introducing New q12h

OxyContin™ (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

The first and only q12h oxycodone.

Brought to you by the makers of MS Contin® Tablets CII (morphine sulfate controlled-release).

Pharmacy Introductory Offer

Receive a stocking rebate on your initial order of OxyContin Tablets purchased during the introductory period: January 1, 1996 to March 29, 1996.

Complete coupon, enclose wholesaler invoice as proof of purchase, and receive rebate directly from Purdue Pharma L.P.

Don't delay! Order your initial supply of OxyContin Tablets today.

Introductory Offer For Pharmacies

Promotional Period: January 1, 1996 to March 29, 1996.
Retailers can earn a stocking rebate on their initial order of OxyContin™ Tablets CII (oxycodone HCl controlled-release).

Store Name _____ Date _____

Address _____

City _____ State _____ ZIP _____

Wholesaler _____ Pharmacist's Signature _____

To receive your rebate, submit a copy of the wholesaler invoice showing your purchase of OxyContin Tablets during the introductory period (January 1, 1996 to March 29, 1996). Mail to Purdue Rebate Offer, P.O. Box 81771, Chicago, IL 60681-0771. This form must be sent with wholesaler invoice. No forms accepted after May 1, 1996. Please allow 4 to 6 weeks for delivery of your check.

MS Contin is a registered trademark of The Purdue Frederick Company.

Promotional Ad Slick

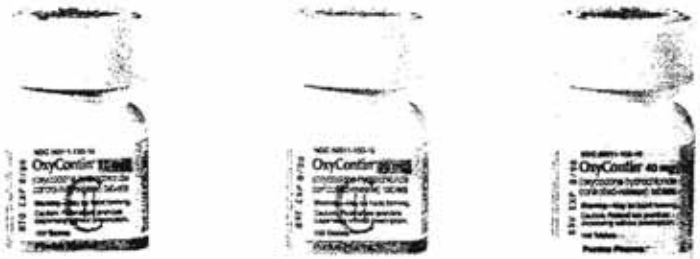
I N T R O D U C I N G

New q12h

OxyContin® II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming



10mg 20mg 40mg

Small, color-coded tablets (actual size)

Strength/Quantity	NDC Number	AWP (100 tablet bottle)	Rebate (per bottle)*	Item #
10mg 100's bottle	59011-100-10	$107.16	$2.00	
20mg 100's bottle	59011-103-10	$205.10	$4.00	
40mg 100's bottle	59011-105-10	$363.91	$6.00	

*Earn an additional $3 rebate for stocking two or more different *strengths* of OxyContin. Maximum rebate allowed is $15 per pharmacy location. This offer not to be combined with any other promotional offer.

Order your initial stock of OxyContin Tablets now. Only orders accompanied by a DEA 222-C form will be processed. **No phone orders accepted.**

OxyContin™ 10 mg Tablets
OxyContin™ 20 mg Tablets
OxyContin™ 40 mg Tablets

CII

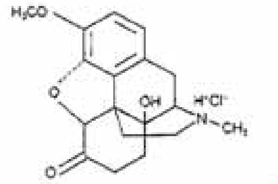
(Oxycodone Hydrochloride Controlled-Release)

WARNING: May Be Habit Forming

A4609-611

DESCRIPTION

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are an opioid analgesic supplied in 10 mg, 20 mg, and 40 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The chemical formula is 4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hydroxypropyl methylcellulose, lactose, magnesium stearate, povidone, red iron oxide (20 mg strength tablet only), stearyl alcohol, talc, titanium dioxide, triacetin, yellow iron oxide (40 mg strength tablet only), and other ingredients.

CLINICAL PHARMACOLOGY

Central Nervous System

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria and feelings of relaxation. Like all pure opioid agonists, there is no ceiling effect to analgesia, such as is seen with partial agonists or non-opioid analgesics.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic. Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration—Efficacy Relationships (Pharmacodynamics)

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects. In normal volunteers these include pupillary constriction, sedation and overall "drug effect" and in patients, analgesia and feelings of "relaxation." In non-tolerant patients, analgesia is not usually seen at a plasma oxycodone concentration of less than 5–10 ng/mL.

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase with repeated dosing due to an increase in pain and/or the development of tolerance.

Concentration—Adverse Experience Relationships

OxyContin™ tablets are associated with typical opioid-related adverse experiences similar to those seen with immediate-release oxycodone and all opioids. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is poorly understood.

As with all opioids, the dose must be individualized (see DOSAGE AND ADMINISTRATION), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

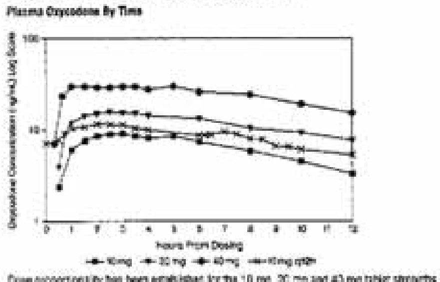
PHARMACOKINETICS AND METABOLISM

The activity of OxyContin™ (oxycodone hydrochloride controlled-release) tablets is primarily due to the parent drug oxycodone. OxyContin tablets are designed to provide controlled delivery of oxycodone over 12 hours. Oxycodone is well absorbed from OxyContin tablets with an oral bioavailability of from 60% to 87%. The relative oral bioavailability of OxyContin to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers, steady-state levels were achieved within 24-36 hours. Dose proportionality has been established for the 10 mg, 20 mg and 40 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers the $t_{1/2}$ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone By Time



Dose proportionality has been established for the 10 mg, 20 mg and 40 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Given the short half-life of elimination of oxycodone from OxyContin, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin tablets than for the immediate-release formulation.

Table 1
Mean [% coefficient variation]

Regimen / Dosage Form	AUC (ng•hr/mL)*	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose				
10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
Multiple Dose				
10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

*for single-dose $AUC = AUC_{0-\infty}$; for multiple-dose $AUC = AUC_{0-T}$

Food Effects

In contrast to immediate-release formulations, food has no significant effect on the absorption of oxycodone from OxyContin. Oxycodone release from OxyContin tablets is pH independent.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen and brain. Oxycodone has been found in breast milk (see PRECAUTIONS).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known at present.

The formation of oxymorphone, but not noroxycodone, is mediated by CYP2D6 and as such its formation can, in theory, be affected by other drugs (see Drug-Drug Interactions).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects. There were no differences in adverse event reporting between young and elderly subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Preliminary data from a study involving patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone 60%, 50% and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour (see PRECAUTIONS).

Hepatic Impairment

Preliminary data from a study involving patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours (see PRECAUTIONS).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part via CYP2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination can be blocked by a variety of drugs (e.g., certain cardiovascular drugs and anti-depressants). Patients receiving such drugs concomitantly with OxyContin do not appear to present different therapeutic profiles than other patients.

CLINICAL TRIALS

OxyContin™ (oxycodone hydrochloride controlled-release) tablets were evaluated in studies involving 713 patients with either cancer or non-cancer pain. All patients receiving OxyContin were dosed q12h. Efficacy comparable to other forms of oral oxycodone was demonstrated in clinical studies using pharmacokinetic, pharmacodynamic and efficacy outcomes. The outcome of these trials indicated: (1) a positive relationship between dose and plasma oxycodone concentration, (2) a positive relationship between plasma oxycodone concentration and analgesia, and (3) an observed peak to trough variation in plasma concentration with OxyContin lying within the observed range established with qid dosing of immediate-release oxycodone in clinical populations at the same total daily dose.

In clinical trials, OxyContin tablets were substituted for a wide variety of analgesics, including acetaminophen (APAP), aspirin (ASA), other non-steroidal anti-inflammatory drugs (NSAIDs), opioid combination products and single-entity opioids, primarily morphine. In cancer patients receiving adequate opioid therapy at baseline, pain intensity scores and acceptability of therapy remained unchanged by transfer to OxyContin. For non-cancer pain patients who had moderate to severe pain at baseline on prn opioid therapy, pain control and acceptability of therapy improved with the introduction of fixed-interval therapy with OxyContin.

Use in Cancer Pain

OxyContin was studied in three double-blind, controlled clinical trials involving 341 cancer patients and several open-label trials with therapy durations of over 10 months.

Two, double-blind, controlled clinical studies indicated that OxyContin dosed q12h produced analgesic efficacy equivalent to immediate-release oxycodone dosed qid at the same total daily dose. Peak and trough plasma concentrations attained were similar to those attained with immediate-release oxycodone at equivalent total daily doses. With titration to analgesic effect and proper use of rescue medication, nearly every patient achieved adequate pain control with OxyContin.

In the third study, a double-blind, active-controlled, crossover trial, OxyContin dosed q12h was shown to be equivalent in efficacy and safety to immediate-release oxycodone dosed qid at the same total daily dose. Patients were able to be titrated to an acceptable analgesic effect with either OxyContin or immediate-release oxycodone with both treatments providing stable pain control within 2 days in most patients.

In patients with cancer pain, the total daily OxyContin doses tested ranged from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Studies in Non-Cancer Pain

A double-blind, placebo-controlled, fixed-dose, parallel group study was conducted in 133 patients with moderate to severe osteoarthritis pain, who were judged as having inadequate pain control with prn opioids and maximal non-steroidal anti-inflammatory therapy. In this study, 20 mg OxyContin q12h significantly decreased pain and improved quality of life, mood and sleep, relative to placebo. Both dose-concentration and concentration-effect relationships were noted with a minimum effective plasma oxycodone concentration of approximately 5–10 ng/mL.

In a double-blind, active-controlled, crossover study involving 57 patients with low-back pain inadequately controlled with prn opioids and non-opioid therapy, OxyContin administered q12h provided analgesia equivalent to immediate-release oxycodone administered qid. Patients could be titrated to an acceptable analgesic effect with either OxyContin or immediate-release forms of oxycodone.

Single-Dose Comparison with Standard Therapy

A single-dose, double-blind, placebo-controlled, post-operative study of 182 patients was conducted utilizing graded doses of OxyContin (10, 20 and 30 mg). Twenty and 30 mg of OxyContin gave equivalent peak analgesic effect compared to two oxycodone 5 mg/acetaminophen 325 mg tablets and to 15 mg immediate-release oxycodone, while the 10 mg dose of OxyContin was intermediate between both the immediate-release and combination products and placebo. The onset of analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery) because the safety or appropriateness of fixed-dose, long-acting opioids in this setting has not been established.

Other Clinical Trials

In open-label trials involving approximately 200 patients with cancer-related and non-cancer pain, dosed according to the package insert recommendations, appropriate analgesic effectiveness was noted without regard to age, gender, race, or disease state. There were no unusual drug interactions observed in patients receiving a wide range of medications common in these populations.

For opioid-naive patients, the average total daily dose of OxyContin was approximately 40 mg per day. There was no evidence of oxycodone and metabolite accumulation during 8 months of therapy. For cancer pain patients the average total daily dose was 105 mg (range 20 to 720 mg) per day. There was a significant decrease in acute opioid-related side effects, except for constipation, during the first several weeks of therapy. Development of significant tolerance to analgesia was uncommon.

INDICATIONS AND USAGE

OxyContin™ tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. (See: CLINICAL PHARMACOLOGY; CLINICAL TRIALS).

CONTRAINDICATIONS

OxyContin™ is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OxyContin™ (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODONE.

Respiratory Depression

Respiratory depression is the chief hazard from all opioid agonist preparations. Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin™, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. OxyContin may produce orthostatic hypotension in ambulatory patients. OxyContin, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are intended for use in patients who require oral pain therapy with an opioid agonist of more than a few days duration. As with any opioid analgesic, it is critical to adjust the dosing regimen individually for each patient (see DOSAGE AND ADMINISTRATION).

Selection of patients for treatment with OxyContin should be governed by the same principles that apply to the use of similar controlled-release opioid analgesics (see INDICATIONS AND USAGE). Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension. Physicians should individualize treatment in every case, using non-opioid analgesics, prn opioids and/or combination products, and chronic opioid therapy with drugs such as OxyContin in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Care Policy and Research, and the American Pain Society.

Use of OxyContin is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin, like all opioid analgesics, should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Patients who are already receiving OxyContin tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given and the temporary changes in physiology caused by the surgical intervention (see PRECAUTIONS: Drug-Drug Interactions, and DOSAGE AND ADMINISTRATION).

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

Significant tolerance should not occur in most of the patients treated with the lowest doses of oxycodone. It should be expected, however, that a fraction of cancer patients will develop some degree of tolerance and require progressively higher dosages of OxyContin to maintain pain control during chronic treatment. Regardless of whether this occurs as a result of increased pain secondary to disease progression or pharmacological tolerance, dosages can usually be increased safely by adjusting the patient's dose to maintain an acceptable balance between pain relief and side effects. The dosage should be selected according to the patient's individual analgesic response and ability to tolerate side effects. Tolerance to the analgesic effect of opioids is usually paralleled by tolerance to side effects, except for constipation.

Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity (see OVERDOSAGE). If OxyContin is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. This is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate or heart rate.

If signs and symptoms of withdrawal occur, patients should be treated by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of OxyContin combined with symptomatic support (see DOSAGE AND ADMINISTRATION: Cessation of Therapy).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin (oxycodone hydrochloride controlled-release) tablets or their caregivers should be given the following information by the physician, nurse, pharmacist or caregiver:

1. Patients should be advised that OxyContin tablets were designed to work properly only if swallowed whole. They may release all their contents at once if broken, chewed or crushed, resulting in a risk of overdose.
2. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
3. Patients should be advised not to adjust the dose of OxyContin without consulting the prescribing professional.

4. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
5. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur.
6. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
7. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
8. Patients should be advised that they may pass empty matrix "ghosts" (tablet) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
9. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Laboratory Monitoring
Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Interactions with Alcohol and Drugs of Abuse
Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs which cause central nervous system depression.

Use in Drug and Alcohol Addiction
OxyContin is an opioid with no approved use in the management of addictive disorders. Its prescribed usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions
Opioid analgesics, including OxyContin, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants
OxyContin, like all opioid analgesics, should be started at ½ to ⅓ of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers and alcohol because respiratory depression, hypotension and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Mutagenicity
Studies of oxycodone in animals to evaluate its carcinogenic and mutagenic potential have not been conducted owing to the length of clinical experience with this drug substance.

Pregnancy
Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg (48 mg/m²) and 125 mg/kg (1375 mg/m²), respectively. These doses are 4 and 60 times a human dose of 120 mg/day (74 mg/m²), based on mg/kg of a 60 kg adult (0.7 and 19 times the human dose based upon mg/m²). The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects—Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Labor and Delivery
OxyContin is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn.

Nursing Mothers
Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin since oxycodone may be excreted in the milk.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 have not been established with this dosage form of oxycodone. However, oxycodone has been used extensively in the pediatric population in other dosage forms, as have the excipients used in this formulation. No specific increased risk is expected from the use of this form of oxycodone in pediatric patients old enough to safely take tablets if dosing is adjusted for the patient's weight (see DOSAGE AND ADMINISTRATION). **It must be remembered that OxyContin tablets cannot be crushed or divided for administration.**

Geriatric Use
In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15%. In clinical trials with appropriate titration of therapy and dose titration, no untoward or unexpected side effects were seen based on age, and the usual doses and dosing intervals are appropriate for the geriatric patient. As with all opioids, the starting dose should be reduced to ½ to ⅓ of the usual dosage in debilitated, non-tolerant patients.

Hepatic Impairment
A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at ½ to ⅓ the usual doses and careful dose titration is warranted.

Renal Impairment
In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences
In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

Serious adverse reactions which may be associated with OxyContin™ (oxycodone hydrochloride controlled-release) tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and to an even lesser degree, circulatory depression, hypotension or shock (see OVERDOSE).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>3%) include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

In clinical trials comparing OxyContin with immediate-release oxycodone and placebo, the most common adverse events (>3%) reported by patients (211) at least once during therapy were:

Table 2

	OxyContin n=327 # pts (%)		Immediate-Release n=225 # pts (%)		Placebo n=45 # pts (%)	
Constipation	52	(23)	58	(26)	3	(7)
Nausea	52	(23)	60	(27)	5	(11)
Somnolence	52	(23)	55	(24)	2	(4)
Dizziness	35	(15)	38	(16)	4	(9)
Pruritus	25	(13)	28	(12)	1	(2)
Vomiting	27	(12)	31	(14)	3	(7)
Headache	17	(7)	19	(8)	3	(7)
Dry Mouth	13	(6)	13	(7)	1	(2)
Asthenia	13	(6)	16	(7)	—	—
Sweating	12	(6)	13	(6)	1	(2)

The following adverse reactions were reported in OxyContin treated patients with an incidence between 1% and 2%, in descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials:

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, peripheral edema, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, speech disorder, stupor, tremor, vertigo, withdrawal syndrome

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis

Special Senses: abnormal vision, taste perversion

Urogenital: dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

DRUG ABUSE AND DEPENDENCE (Addiction)

OxyContin™ is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Iatrogenic "addiction" to opioids legitimately used in the management of pain is very rare. "Drug seeking" behavior is very common to addicts. Tolerance and physical dependence in pain patients are not signs of psychological dependence. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Most chronic pain patients limit their intake of opioids to achieve a balance between the benefits of the drug and dose-limiting side effects.

Physicians should be aware that psychological dependence may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true psychological dependence and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin consists of a dual-polymer matrix intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OxyContin™. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles
OxyContin™ (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODONE.

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin is intended for the management of moderate to severe pain in patients who require treatment with an oral opioid analgesic for more than a few days. This controlled-release nature of the formulation allows it to be effectively administered every 12 hours. (See CLINICAL PHARMACOLOGY: PHARMACOKINETICS AND METABOLISM.) While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their own patient. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Initiation of Therapy
It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:
(1) the general condition and medical status of the patient
(2) the daily dose, potency and kind of the analgesic(s) the patient has been taking
(3) the reliability of the conversion estimate used to calculate the dose of oxycodone
(4) the patient's opioid exposure and opioid tolerance (if any)
(5) the balance between pain control and adverse experiences

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see PRECAUTIONS: Drug-Drug Interactions).

Patients Not Already Taking Opioids (opioid naive)
Clinical trials have shown that patients may initiate analgesic therapy with OxyContin. A reasonable starting dose for most patients who are opioid naive is 10 mg q12h. If a non-opioid analgesic (aspirin (ASA), acetaminophen (APAP) or a non-steroidal anti-inflammatory (NSAID)) is being provided, it may be continued. If the current non-opioid is discontinued, early upward dose titration may be necessary.

Conversion from Fixed-Ratio Opioid/APAP, ASA, or NSAID Combination Drugs
Patients who are taking 1 to 5 tablets/capsules/caplets per day of a regular strength fixed-combination opioid/non-opioid should be started on 10 to 20 mg OxyContin q12h. For patients taking 6 to 9 tablets/capsules/ caplets, a starting dose of 20 to 30 mg q12h is suggested. For those taking 10 to 12 tablets, caplets or capsules a day, 30 to 40 mg q12h should be considered. The non-opioid may be continued as a separate drug. Alternatively, a different non-opioid analgesic may be selected. If the decision is made to discontinue the non-opioid analgesic, consideration should be given to early upward titration.

Patients Currently on Opioid Therapy
If a patient has been receiving opioid-containing medications prior to OxyContin therapy, the total daily (24-hour) dose of the other opioids should be determined.

1. Using standard conversion ratio estimates (see Table 3 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. Divide this 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.
3. Round down to a dose which is appropriate for the tablet strengths available (10, 20, and 40 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.

No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 3 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 3

*Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone**

(Mg/Day Prior Opioid x Factor=Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codeine	0.15	—
Fentanyl TTS	SEE BELOW	SEE BELOW
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

*To be used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of immediate-release oral oxycodone or another suitable short-acting analgesic.

OxyContin can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see PRECAUTIONS).

Conversion from Transdermal Fentanyl to OxyContin
Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 µg/hr fentanyl transdermal patch. The patient should be followed closely for early titration as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences
Most patients receiving opioids, especially those who are opioid naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and promptly, typically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and it is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyContin may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage
Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Rescue medication should be available (see Supplemental Analgesia). Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the health-care team, the patient and the caregiver/family.

Supplemental Analgesia
Most cancer patients given around-the-clock therapy with controlled-release opioids will need to have immediate-release medication available for "rescue" from breakthrough pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Rescue medication can be immediate-release oxycodone, either alone or in combination with acetaminophen, aspirin or other NSAIDs as a supplemental analgesic. The supplemental analgesic should be prescribed at ½ to ⅓ of the 12-hour OxyContin dose as shown in Table 4. The rescue medication is dosed as needed for breakthrough pain and administered one hour before anticipated incident pain. If more than two doses of rescue medications are needed within 24 hours, the dose of OxyContin should be titrated upward. Caregivers and patients using prn rescue analgesia in combination with around-the-clock opioids should be advised to report incidents of breakthrough pain to the physician managing the patient's analgesia (see Information for Patients/Caregivers).

Table 4

Table of Appropriate Supplemental Analgesia

OxyContin q12h Dose (mg)	prn Rescue Dose immediate-release oxycodone (mg)
10 (1×10 mg)	5
20 (2×10 mg)	5
30 (3×10 mg)	10
40 (2×20 mg)	10
60 (3×20 mg)	15
80 (2×40 mg)	20
120 (3×40 mg)	30

Maintenance of Therapy
The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy
When the patient no longer requires therapy with OxyContin tablets, patients receiving doses of 20–60 mg/day can usually have the therapy stopped abruptly without incident. However, higher doses should be tapered over several days to prevent signs and symptoms of withdrawal in the physically dependent patient. The daily dose should be reduced by approximately 50% for the first two days and then reduced by 25% every two days thereafter until the total dose reaches the dose recommended for opioid naive patients (10 or 20 mg q12h). Therapy can then be discontinued.

If signs of withdrawal appear, tapering should be stopped. The dose should be slightly increased until the signs and symptoms of opioid withdrawal disappear. Tapering should then begin again but with longer periods of time between each dose reduction.

Conversion from OxyContin to Parenteral Opioids
To avoid overdose, conservative dose conversion ratios should be followed. Initiate treatment with about 50% of the estimated equianalgesic daily dose of parenteral opioid divided into suitable individual doses based on the appropriate dosing interval, and titrate based upon the patient's response.

SAFETY AND HANDLING

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

HOW SUPPLIED

OxyContin™ (oxycodone hydrochloride controlled-release) 10 mg tablets are round, unscored, white-colored, convex tablets bearing the symbol OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100

OxyContin (oxycodone hydrochloride controlled-release) 20 mg tablets are round, unscored, pink-colored, convex tablets bearing the symbol OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100

OxyContin (oxycodone hydrochloride controlled-release) 40 mg tablets are round, unscored, yellow-colored, convex tablets bearing the symbol OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100

Store tablets at controlled room temperature 15–30°C (59–86°F).

Dispense in tight, light-resistant container.

CAUTION

DEA Order Form Required.

Federal law prohibits dispensing without prescription.

Manufactured by The PF Laboratories, Inc.
Totowa, N.J. 07512

Distributed by Purdue Pharma L.P.
Norwalk, CT 06850-3590

December 5, 1995
A4909-B11

I N T R O D U C I N G

New q12h

OxyContin® II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

10mg 20mg 40mg

Small, color-coded tablets (actual size)

Strength/Quantity	NDC Number	AWP (100 tablet bottle)	Rebate (per bottle)*	Item #
10mg 100's bottle	59011-100-10	$107.16	$2.00	
20mg 100's bottle	59011-103-10	$205.10	$4.00	
40mg 100's bottle	59011-105-10	$363.91	$6.00	

*Earn an additional $3 rebate for stocking two or more different *strengths* of OxyContin. Maximum rebate allowed is $15 per pharmacy location. This offer not to be combined with any other promotional offer.

Order your initial stock of OxyContin Tablets now. Only orders accompanied by a DEA 222-C form will be processed. **No phone orders accepted.**

INTRODUCING

New

OxyContin® CII

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

Heavy promotional support planned.

—Promoted by over 300 dedicated professionals—the same sales force that boosted sales of MS Contin® (morphine sulfate controlled-release) Tablets to over $100 million.*

—Journal advertising and direct mail to doctors, nurses, pharmacists, hospitals, hospices, and managed care organizations.

Pharmacy Introductory Offer

Receive a stocking rebate on your initial order of OxyContin Tablets purchased during the introductory period: January 1, 1996 to March 29, 1996.

Complete coupon on other side, enclose wholesaler invoice as proof of purchase, and receive rebate directly from Purdue Pharma L.P.

Don't delay! Order your initial supply of OxyContin Tablets today.

*12-month sales of noninjectable Class II and Class III opioid analgesics through October 1995. *IMS Drug Store and Hospital Audit*, October 1995.

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

OxyContin™ 10 mg Tablets
OxyContin™ 20 mg Tablets
OxyContin™ 40 mg Tablets

CII

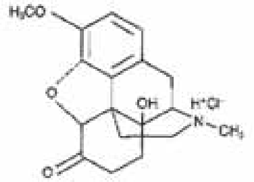
(Oxycodone Hydrochloride Controlled-Release)

WARNING: May Be Habit Forming

44692-011

DESCRIPTION

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are an opioid analgesic supplied in 10 mg, 20 mg, and 40 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The chemical formula is 4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hydroxypropyl methylcellulose, lactose, magnesium stearate, povidone, red iron oxide (20 mg strength tablet only), stearyl alcohol, talc, titanium dioxide, triacetin, yellow iron oxide (40 mg strength tablet only), and other ingredients.

CLINICAL PHARMACOLOGY

Central Nervous System

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria and feelings of relaxation. Like all pure opioid agonists, there is no ceiling effect to analgesia, such as is seen with partial agonists or non-opioid analgesics.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic. Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration—Efficacy Relationships (Pharmacodynamics)

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects. In normal volunteers these include pupillary constriction, sedation and overall "drug effect" and in patients, analgesia and feelings of "relaxation." In non-tolerant patients, analgesia is not usually seen at a plasma oxycodone concentration of less than 5–10 ng/mL.

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase with repeated dosing due to an increase in pain and/or the development of tolerance.

Concentration—Adverse Experience Relationships

OxyContin™ tablets are associated with typical opioid-related adverse experiences similar to those seen with immediate-release oxycodone and all opioids. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is poorly understood.

As with all opioids, the dose must be individualized (see DOSAGE AND ADMINISTRATION), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

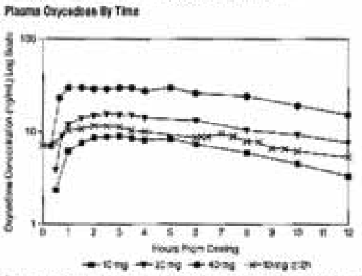
PHARMACOKINETICS AND METABOLISM

The activity of OxyContin™ (oxycodone hydrochloride controlled-release) tablets is primarily due to the parent drug oxycodone. OxyContin tablets are designed to provide controlled delivery of oxycodone over 12 hours. Oxycodone is well absorbed from OxyContin tablets with an oral bioavailability of from 60% to 87%. The relative oral bioavailability of OxyContin to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers, steady-state levels were achieved within 24–36 hours. Dose proportionality has been established for the 10 mg, 20 mg and 40 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers the $t_{1/2}$ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone By Time



Dose proportionality has been established for the 10 mg, 20 mg and 40 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Given the short half-life of elimination of oxycodone from OxyContin, steady-state plasma concentrations are achieved within 24–36 hours of initiation of dosing with OxyContin tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours the two treatments were found to be equivalent for AUC and C_{max} and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin tablets than for the immediate-release formulation.

Table 1
Mean [% coefficient variation]

Regimen/ Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose 10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
Multiple Dose 10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

†for single-dose AUC = AUC_{0-inf}; for multiple-dose AUC = AUC_{0-T}

Food Effects

In contrast to immediate-release formulations, food has no significant effect on the absorption of oxycodone from OxyContin. Oxycodone release from OxyContin tablets is pH independent.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen and brain. Oxycodone has been found in breast milk (see PRECAUTIONS).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known at present.

The formation of oxymorphone, but not noroxycodone, is mediated by CYP2D6 and as such its formation can, in theory, be affected by other drugs (see Drug-Drug Interactions).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects. There were no differences in adverse event reporting between young and elderly subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Preliminary data from a study involving patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone 60%, 50% and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour (see PRECAUTIONS).

Hepatic Impairment

Preliminary data from a study involving patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other drug effects. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours (see PRECAUTIONS).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part via CYP2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination can be blocked by a variety of drugs (e.g., certain cardiovascular drugs and anti-depressants). Patients receiving such drugs concomitantly with OxyContin do not appear to present different therapeutic profiles than other patients.

CLINICAL TRIALS

OxyContin™ (oxycodone hydrochloride controlled-release) tablets were evaluated in studies involving 713 patients with either cancer or non-cancer pain. All patients receiving OxyContin were dosed q12h. Efficacy comparable to other forms of oral oxycodone was demonstrated in clinical studies using pharmacokinetic, pharmacodynamic and efficacy outcomes. The outcome of these trials indicated: (1) a positive relationship between dose and plasma oxycodone concentration, (2) a positive relationship between plasma oxycodone concentration and analgesia, and (3) an observed peak to trough variation in plasma concentration with OxyContin lying within the observed range established with qid dosing of immediate-release oxycodone in clinical populations at the same total daily dose.

In clinical trials, OxyContin tablets were substituted for a wide variety of analgesics, including acetaminophen (APAP), aspirin (ASA), other non-steroidal anti-inflammatory drugs (NSAIDs), opioid combination products and single-entity opioids, primarily morphine. In cancer patients receiving adequate opioid therapy at baseline, pain intensity scores and acceptability of therapy remained unchanged by transfer to OxyContin. For non-cancer pain patients who had moderate to severe pain at baseline on prn opioid therapy, pain control and acceptability of therapy improved with the introduction of fixed-interval therapy with OxyContin.

Use in Cancer Pain

OxyContin was studied in three double-blind, controlled clinical trials involving 341 cancer patients and several open-label trials with therapy durations of over 10 months.

Two, double-blind, controlled clinical studies indicated that OxyContin dosed q12h produced analgesic efficacy equivalent to immediate-release oxycodone dosed qid at the same total daily dose. Peak and trough plasma concentrations attained were similar to those attained with immediate-release oxycodone at equivalent total daily doses. With titration to analgesic effect and proper use of rescue medication, nearly every patient achieved adequate pain control with OxyContin.

In the third study, a double-blind, active-controlled, crossover trial, OxyContin dosed q12h was shown to be equivalent in efficacy and safety to immediate-release oxycodone dosed qid at the same total daily dose. Patients were able to be titrated to an acceptable analgesic effect with either OxyContin or immediate-release oxycodone with both treatments providing stable pain control within 2 days in most patients.

In patients with cancer pain, the total daily OxyContin doses tested ranged from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Studies in Non-Cancer Pain

A double-blind, placebo-controlled, fixed-dose, parallel group study was conducted in 133 patients with moderate to severe osteoarthritis pain, who were judged as having inadequate pain control with prn opioids and maximal non-steroidal anti-inflammatory therapy. In this study, 20 mg OxyContin q12h significantly decreased pain and improved quality of life, mood and sleep, relative to placebo. Both dose-concentration and concentration-effect relationships were noted with a minimum effective plasma oxycodone concentration of approximately 5–10 ng/mL.

In a double-blind, active-controlled, crossover study involving 57 patients with low-back pain inadequately controlled with prn opioids and non-opioid therapy, OxyContin administered q12h provided analgesia equivalent to immediate-release oxycodone administered qid. Patients could be titrated to an acceptable analgesic effect with either OxyContin or immediate-release forms of oxycodone.

Single-Dose Comparison with Standard Therapy

A single-dose, double-blind, placebo-controlled, post-operative study of 182 patients was conducted utilizing graded doses of OxyContin (10, 20 and 30 mg). Twenty and 30 mg of OxyContin gave equivalent peak analgesic effect compared to two oxycodone 5 mg/acetaminophen 325 mg tablets and to 15 mg immediate-release oxycodone, while the 10 mg dose of OxyContin was intermediate between both the immediate-release and combination products and placebo. The onset of analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery) because the safety or appropriateness of fixed-dose, long-acting opioids in this setting has not been established.

Other Clinical Trials

In open-label trials involving approximately 200 patients with cancer-related and non-cancer pain, dosed according to the package insert recommendations, appropriate analgesic effectiveness was noted without regard to age, gender, race, or disease state. There were no unusual drug interactions observed in patients receiving a wide range of medications common in these populations.

In open-label clinical trials, the average total daily dose of OxyContin was approximately 40 mg per day. There was no evidence of oxycodone and metabolite accumulation during 8 months of therapy. For cancer pain patients the average total daily dose was 105 mg (range 20 to 730 mg) per day. There was a significant decrease in acute opioid-related side effects, except for constipation, during the first several weeks of therapy. Development of significant tolerance to analgesia was uncommon.

INDICATIONS AND USAGE

OxyContin™ tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. (See: CLINICAL PHARMACOLOGY; CLINICAL TRIALS).

CONTRAINDICATIONS

OxyContin™ is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OxyContin™ (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODONE.

Respiratory Depression

Respiratory depression is the chief hazard from all opioid agonist preparations. Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin™, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. OxyContin may produce orthostatic hypotension in ambulatory patients. OxyContin, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are intended for use in patients who require oral pain therapy with an opioid agonist of more than a few days duration. As with any opioid analgesic, it is critical to adjust the dosing regimen individually for each patient (see DOSAGE AND ADMINISTRATION).

Selection of patients for treatment with OxyContin should be governed by the same principles that apply to the use of similar controlled-release opioid analgesics (see INDICATIONS AND USAGE). Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension. Physicians should individualize treatment in every case, using non-opioid analgesics, prn opioids and/or combination products, and chronic opioid therapy with drugs such as OxyContin in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Care Policy and Research, and the American Pain Society.

Use of OxyContin is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin, like all opioid analgesics, should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Patients who are already receiving OxyContin tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given and the temporary changes in physiology caused by the surgical intervention (see PRECAUTIONS: Drug-Drug Interactions, and DOSAGE AND ADMINISTRATION).

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

Significant tolerance should not occur in most of the patients treated with the lowest doses of oxycodone. It should be expected, however, that a fraction of cancer patients will develop some degree of tolerance and require progressively higher dosages of OxyContin to maintain pain control during chronic treatment. Regardless of whether this occurs as a result of increased pain secondary to disease progression or pharmacological tolerance, dosages can usually be increased safely by adjusting the patient's dose to maintain an acceptable balance between pain relief and side effects. The dosage should be selected according to the patient's individual analgesic response and ability to tolerate side effects. Tolerance to the analgesic effect of opioids is usually paralleled by tolerance to side effects, except for constipation.

Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity (see OVERDOSAGE). If OxyContin is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. This is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate or heart rate.

If signs and symptoms of withdrawal occur, patients should be treated by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of OxyContin combined with symptomatic support (see DOSAGE AND ADMINISTRATION: Cessation of Therapy).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin (oxycodone hydrochloride controlled-release) tablets or their caregivers should be given the following information by the physician, nurse, pharmacist or caregiver:

1. Patients should be advised that OxyContin tablets were designed to work properly only if swallowed whole. They may release all their contents at once if broken, chewed or crushed, resulting in a risk of overdose.
2. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
3. Patients should be advised not to adjust the dose of OxyContin without consulting the prescribing professional.

4. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
5. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur.
6. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
7. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
8. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
9. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs which cause central nervous system depression.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at ⅓ to ½ of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers and alcohol because respiratory depression, hypotension and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Mutagenicity

Studies of oxycodone in animals to evaluate its carcinogenic and mutagenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Pregnancy

Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg (48 mg/m²) and 125 mg/kg (1375 mg/m²), respectively. These doses are 4 and 80 times a human dose of 120 mg/day (74 mg/m²), based on mg/kg of a 60 kg adult (2.7 and 19 times the human dose based upon mg/m²). The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects—Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Labor and Delivery

OxyContin is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin since oxycodone may be excreted in the milk.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established with this dosage form of oxycodone. However, oxycodone has been used extensively in the pediatric population in other dosage forms, as have the excipients used in this formulation. No specific increased risk is expected from the use of this form of oxycodone in pediatric patients old enough to safely take tablets if dosing is adjusted for the patient's weight (see DOSAGE AND ADMINISTRATION). **It must be remembered that OxyContin tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15%. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen based on age, and the usual doses and dosing intervals are appropriate for the geriatric patient. As with all opioids, the starting dose should be reduced to ⅓ to ½ of the usual dosage in debilitated, non-tolerant patients.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at ⅓ to ½ the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

Serious adverse reactions which may be associated with OxyContin™ (oxycodone hydrochloride controlled-release) tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension or shock (see OVERDOSE).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

In clinical trials comparing OxyContin with immediate-release oxycodone and placebo, the most common adverse events (>5%) reported by patients (pts) at least once during therapy were:

Table 2

	OxyContin n=227 # pts	(%)	Immediate-Release n=225 # pts	(%)	Placebo n=45 # pts	(%)
Constipation	52	(23)	56	(25)	3	(7)
Nausea	52	(23)	60	(27)	5	(11)
Somnolence	52	(23)	55	(24)	2	(4)
Dizziness	29	(13)	35	(16)	4	(9)
Pruritus	29	(13)	28	(12)	1	(2)
Vomiting	27	(12)	31	(14)	3	(7)
Headache	17	(7)	19	(8)	3	(7)
Dry Mouth	13	(6)	15	(7)	1	(2)
Asthenia	13	(6)	16	(7)	—	—
Sweating	12	(5)	13	(6)	1	(2)

The following adverse experiences were reported in OxyContin treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials.

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, peripheral edema, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis

Special Senses: abnormal vision, taste perversion

Urogenital: dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

DRUG ABUSE AND DEPENDENCE (Addiction)

OxyContin™ is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Iatrogenic "addiction" to opioids legitimately used in the management of pain is very rare. "Drug seeking" behavior is very common in addicts. Tolerance and physical dependence in pain patients are not signs of psychological dependence. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Most chronic pain patients limit their intake of opioids to achieve a balance between the benefits of the drug and dose-limiting side effects.

Physicians should be aware that psychological dependence may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true psychological dependence and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin consists of a dual-polymer matrix, intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OxyContin™. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OxyContin™ (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODONE.

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin is intended for the management of moderate to severe pain in patients who require treatment with an oral opioid analgesic for more than a few days. The controlled-release nature of the formulation allows it to be effectively administered every 12 hours. (See CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM.) While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient
(2) the daily dose, potency and kind of the analgesic(s) the patient has been taking
(3) the reliability of the conversion estimate used to calculate the dose of oxycodone
(4) the patient's opioid exposure and opioid tolerance (if any)
(5) the balance between pain control and adverse experiences

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see PRECAUTIONS: Drug-Drug Interactions).

Patients Not Already Taking Opioids (opioid naive)

Clinical trials have shown that patients may initiate analgesic therapy with OxyContin. A reasonable starting dose for most patients who are opioid naive is 10 mg q12h. If a non-opioid analgesic (aspirin (ASA), acetaminophen (APAP) or a non-steroidal anti-inflammatory (NSAID)) is being provided, it may be continued. If the current non-opioid is discontinued, early upward dose titration may be necessary.

Conversion from Fixed-Ratio Opioid/APAP, ASA, or NSAID Combination Drugs

Patients who are taking 1 to 5 tablets/capsules/caplets per day of a regular strength fixed-combination opioid/non-opioid should be started on 10 to 20 mg OxyContin q12h. For patients taking 6 to 9 tablets/capsules/ caplets, a starting dose of 20 to 30 mg q12h is suggested. For those taking 10 to 12 tablets, caplets or capsules a day, 30 to 40 mg q12h should be considered. The non-opioid may be continued as a separate drug. Alternatively, a different non-opioid analgesic may be selected. If the decision is made to discontinue the non-opioid analgesic, consideration should be given to early upward titration.

Patients Currently on Opioid Therapy

If a patient has been receiving opioid-containing medications prior to OxyContin therapy, the total daily (24-hour) dose of the other opioids should be determined.

1. Using standard conversion ratio estimates (see Table 3 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. Divide this 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.
3. Round down to a dose which is appropriate for the tablet strengths available (10, 20, and 40 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.

No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 3 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 3

*Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone**

(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codeine	0.15	—
Fentanyl TTS	SEE BELOW	SEE BELOW
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

*To be used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of immediate-release oral oxycodone or another suitable short-acting analgesic.

OxyContin can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see PRECAUTIONS).

Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 μg/hr fentanyl transdermal patch. The patient should be followed closely for early titration as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyContin may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Rescue medication should be available (see: Supplemental Analgesia). Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the health-care team, the patient and the caregiver/family.

Supplemental Analgesia

Most cancer patients given around-the-clock therapy with controlled-release opioids will need to have immediate-release medication available for "rescue" from breakthrough pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Rescue medication can be immediate-release oxycodone, either alone or in combination with acetaminophen, aspirin or other NSAIDs as a supplemental analgesic. The supplemental analgesic should be prescribed at ¼ to ⅓ of the 12-hour OxyContin dose as shown in Table 4. The rescue medication is dosed as needed for breakthrough pain and administered one hour before anticipated incident pain. If more than two doses of rescue medication are needed within 24 hours, the dose of OxyContin should be titrated upward. Caregivers and patients using prn rescue analgesia in combination with around-the-clock opioids should be advised to report incidents of breakthrough pain to the physician managing the patient's analgesia (see Information for Patients/Caregivers).

Table 4

Table of Appropriate Supplemental Analgesia

OxyContin q12h Dose (mg)	prn Rescue Dose immediate-release oxycodone (mg)
10 (1×10 mg)	5
20 (2×10 mg)	5
30 (3×10 mg)	10
40 (2×20 mg)	10
60 (3×20 mg)	15
80 (2×40 mg)	20
120 (3×40 mg)	30

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with OxyContin tablets, patients receiving doses of 20–60 mg/day can usually have the therapy stopped abruptly without incident. However, higher doses should be tapered over several days to prevent signs and symptoms of withdrawal in the physically dependent patient. The daily dose should be reduced by approximately 50% for the first two days and then reduced by 25% every two days thereafter until the total dose reaches the dose recommended for opioid naive patients (10 or 20 mg q12h). Therapy can then be discontinued.

If signs of withdrawal appear, tapering should be stopped. The dose should be slightly increased until the signs and symptoms of opioid withdrawal disappear. Tapering should then begin again but with longer periods of time between each dose reduction.

Conversion from OxyContin to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed. Initiate treatment with about 50% of the estimated equianalgesic daily dose of parenteral opioid divided into suitable individual doses based on the appropriate dosing interval, and titrate based upon the patient's response.

SAFETY AND HANDLING

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

HOW SUPPLIED

OxyContin™ (oxycodone hydrochloride controlled-release) 10 mg tablets are round, unscored, white-colored, convex tablets bearing the symbol OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100

OxyContin (oxycodone hydrochloride controlled-release) 20 mg tablets are round, unscored, pink-colored, convex tablets bearing the symbol OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100

OxyContin (oxycodone hydrochloride controlled-release) 40 mg tablets are round, unscored, yellow-colored, convex tablets bearing the symbol OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100

Store tablets at controlled room temperature 15–30°C (59–86°F).

Dispense in tight, light-resistant container.

CAUTION

DEA Order Form Required.

Federal law prohibits dispensing without prescription.

Manufactured by The PF Laboratories, Inc.
Totowa, N.J. 07512

Distributed by Purdue Pharma L.P.
Norwalk, CT 06850-3590

U.S. Patent Numbers 4,861,598; 4,970,075; and 5,266,331

December 6, 1995
A4929-611

10mg 20mg 40mg

Small, color-coded tablets (actual size)

New OxyContin® (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

Strength/Quantity	NDC Number	AWP (100 tablet bottle)	Rebate (per bottle)*	Wholesaler Item #
10mg 100's bottle	59011-100-10	$107.16	$2.00	
20mg 100's bottle	59011-103-10	$205.10	$4.00	
40mg 100's bottle	59011-105-10	$363.91	$6.00	

*Earn an additional $3 rebate for stocking two or more different *strengths* of OxyContin. Maximum rebate is $15 per pharmacy location. This offer not to be combined with any other promotional offer.

Order your initial stock of OxyContin Tablets now. Only orders accompanied by a DEA 222-C form will be processed. No phone orders accepted.

Introductory Offer For Pharmacies

Promotional Period: January 1,1996 to March 29,1996.
Earn a stocking rebate on your initial order of OxyContin Tablets.

Store Name _____ Date _____

Address _____

City _____ State _____ ZIP _____

Wholesaler _____ Pharmacist's Signature _____

To receive your rebate, submit a copy of the wholesaler invoice showing your purchase of OxyContin Tablets during the introductory period (January 1,1996 to March 29,1996). Mail to Purdue Rebate offer, P.O. Box 81771, Chicago, IL 60681-0771. This form must be sent with wholesaler invoice. No forms accepted after May 1, 1996. Please allow 4 to 6 weeks for delivery of your check.

MS Contin is a registered trademark of The Purdue Frederick Company.

Please see full prescribing information on inside pages.

 A4916455 000P08 PUR33061

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

Q12h

OxyContin™ (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

The analgesic efficacy of immediate-release oxycodone. The ease of q12h dosing.

Steady-state blood levels achieved within 24-36 hours—allows titration every 1 to 2 days, if necessary

No "ceiling" to analgesic efficacy—may be titrated upward when clinically necessary

In a multicenter clinical study*...

— Titration enhanced efficacy of therapy—only 3.5% of patients discontinued due to inadequate pain control when allowed to titrate and use rescue medication

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

*Data on file, Purdue Pharma L.P.

OxyContin Titration Guide

The goal of titration:

To effectively control pain with two or fewer rescue doses per day.

	OxyContin Tablets q12h dose	Immediate-Release (IR) Oxycodone dose for rescue†	
10mg	10mg q12h	5mg	Titrate the OxyContin dose if more than two rescue doses per day are needed.
	20mg q12h	5mg	
	30mg q12h	10mg	
20mg	40mg q12h	10mg	
	60mg q12h	15mg	
40mg	80mg q12h	20mg	
	120mg q12h	30mg	
Continue titrating, if necessary, using the T • I • M • E principles below.			

Titrate patients every 1 to 2 days, if necessary.

Increase the dose by 25% to 50%, if necessary*; do not increase the dosing frequency.

Manage breakthrough pain with IR oxycodone† at ¼ to ⅓ of the 12-hour OxyContin dose.*

Elevate the OxyContin dose if more than two rescue doses are required per day.

*For patients taking OxyContin 10mg q12h:
— The next titration step should be 20mg q12h
— Breakthrough pain should be managed with IR oxycodone 5mg

†See professional prescribing information for immediate-release oxycodone.

Small, color-coded tablets (actual size)

Q12h

OXYCONTIN® (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

Please see accompanying professional prescribing information.

Oral Analgesics for Moderate to Severe Pain
Tablets Only
Conversion From Oral And Transdermal Analgesics
Tablets Only
12h
OxyContin
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
Warning
The longest-lasting oxycodone ever.
Convenient q12h schedule—won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
Single-entity agent—contains no aspirin or acetaminophen, which may be potentially toxic in maximal daily doses
10mg
20mg
40mg
Actual Size
Small, color-coded tablets—easy to identify and swallow
Variety of strengths—permits precise titration to an effective dose
Massage breakthrough or incident pain with immediate-release (IR) oxycodone—avoids polypharmacy
OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.
Please see accompanying professional prescribing information
Job No. PUR 33043
Page 1
Proof 3
Date 1/30/96
LYONS LAVEY NICKEL SWIFT
PANEL B
PANEL C
PANEL D

PANEL A

Converting From Parenteral And Transdermal Analgesics To OxyContin Tablets Only

Converting From OxyContin Tablets Only

OxyContin Conversion Calculator

Oral Analgesics To OxyContin Tablets Only

q12h OxyContin

Consistent q12h schedule—won't interfere with patients' daytime activities or nighttime rest, and encourages compliance

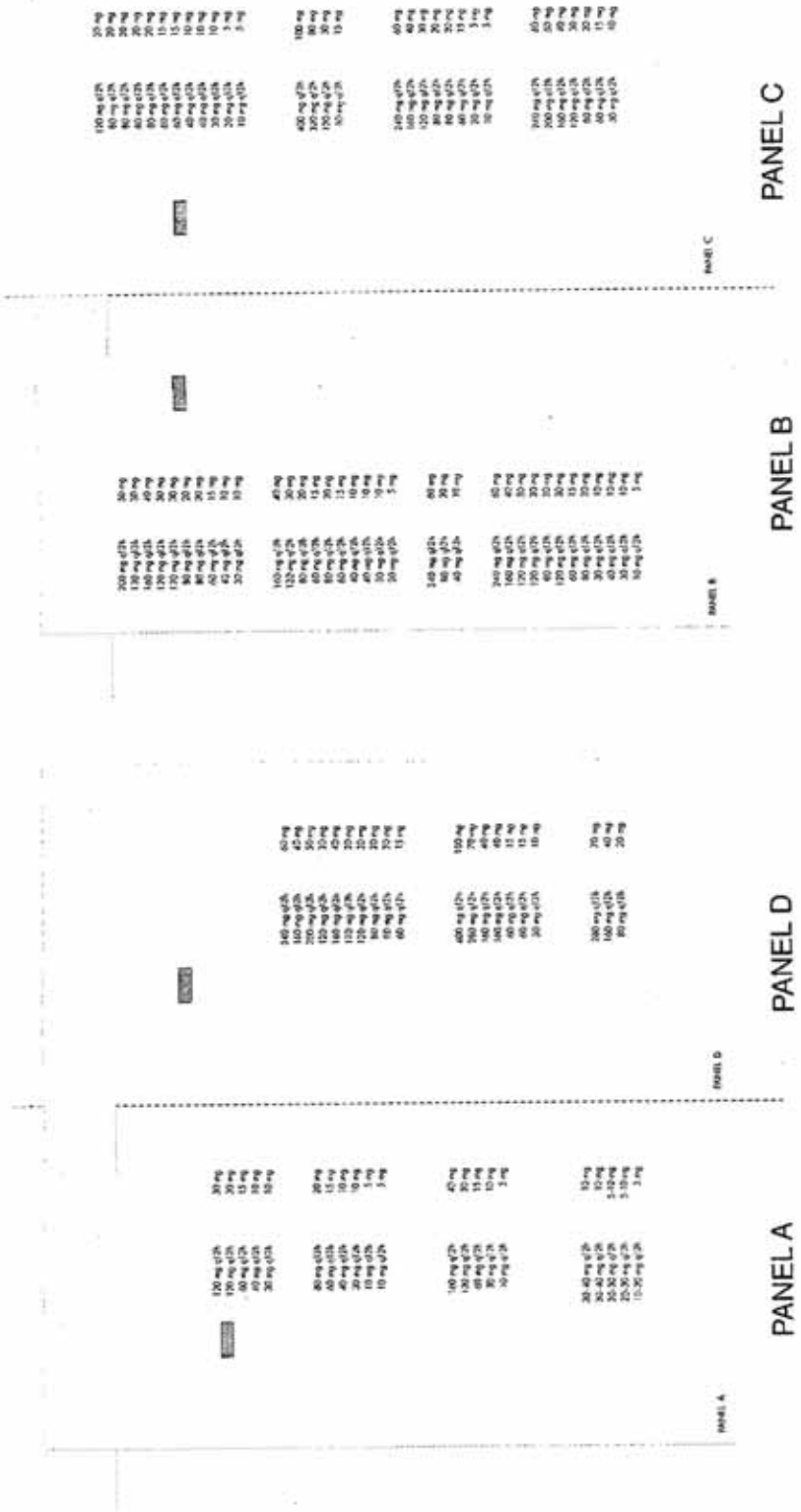
Single-entity agent—contains no opium or acetaminophen, which may be potentially toxic in maximal daily doses

10mg 20mg 40mg

Actual Size

For patients with moderate to severe pain requiring opioid therapy for more than a few days

q12h OxyContin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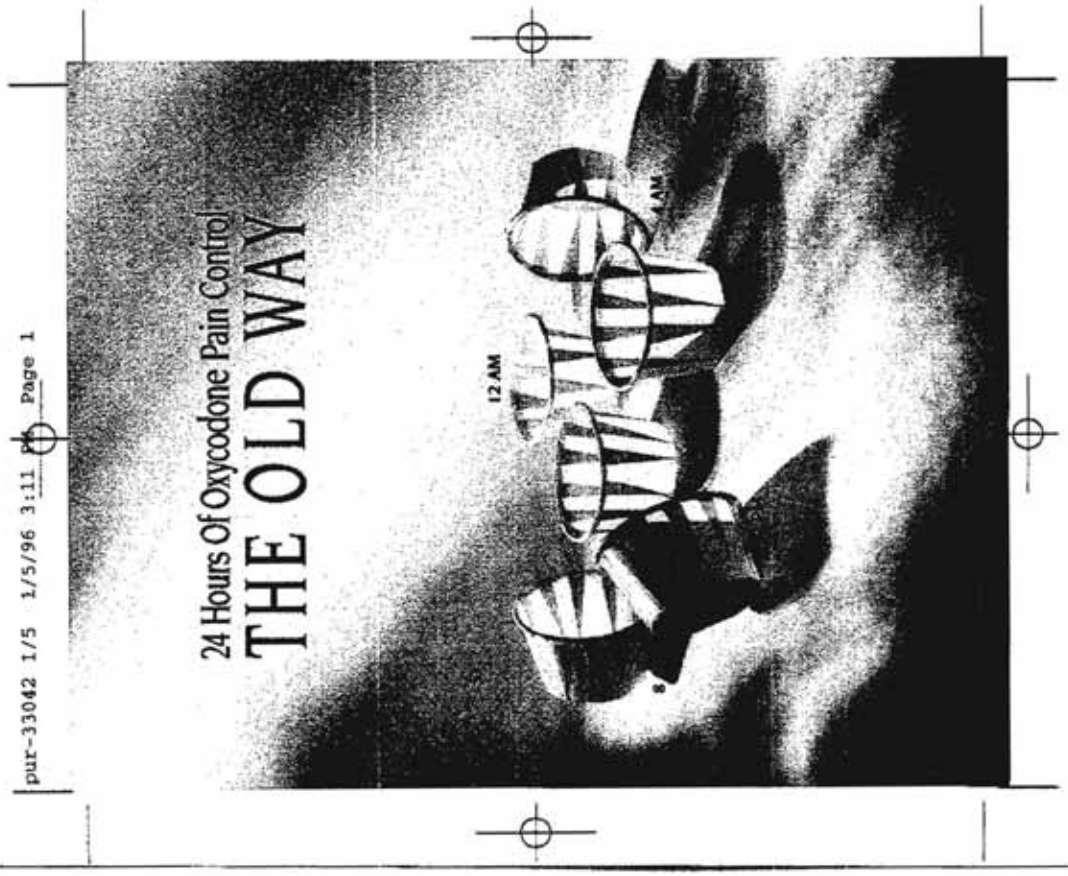
PANEL B
PANEL D
PANEL A


pur-33042 1/5 1/5/96 3:11 PM Page 1
24 Hours Of Oxycodone Pain Control
THE OLD WAY
12 AM
4 AM

pur-33042 1/5 1/5/96 3:13 PM Page 2

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

Introducing New q12h OxyContin® (II) (OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

The analgesic efficacy of immediate-release oxycodone
The ease of q12h dosing

Twelve hours of smooth and reliable pain control—less frequent dosing than with Percocet®, Vicodin®, or Tylenol® with Codeine

Analgesic onset within 1 hour—in most patients

Single-entity agent—contains no aspirin or acetaminophen which may be potentially toxic in maximal daily doses

No "ceiling" to analgesic efficacy—may be titrated upward when clinically necessary

Common opioid side effects—often diminishing over time for many patients, except for constipation

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

Percocet is a registered trademark of The DuPont Merck Pharmaceutical Co.
Vicodin is a registered trademark of Knoll Pharmaceutical Company.
Tylenol with Codeine is a registered trademark of McNeil Pharmaceutical.

OxyContin™

The longest-lasting oxycodone ever.

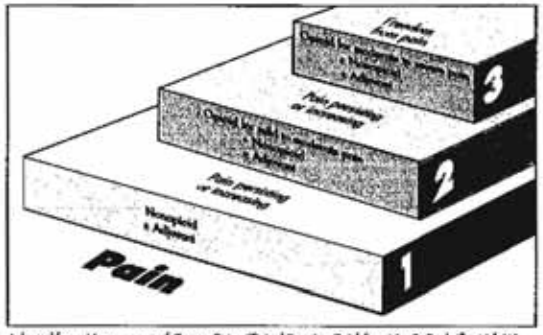
Please see brief summary of prescribing information on adjacent page.

For patients with moderate to severe pain requiring opioid therapy for more than a few days

OxyContin® THE ONE TO START WITH (A-T-C).

The logical next step for patients, with persistent pain, no longer responding to or tolerating nonopioids:

Add to or replace nonopioid with OxyContin.



Adapted from *Management of Cancer Pain. Clinical Practice Guideline.* No. 9. Rockville, Md: US Dept of Health and Human Services AHCPR publication 94-0592. Public Health Service, Agency for Health Care Policy and Research; March 1994.

Please see professional prescribing information on last pages.

Q12h OxyContin—
ideal for initial around-the-clock (A-T-C) opioid therapy.

- Twelve hours of smooth and reliable pain control—less frequent dosing than with short-acting products such as Percocet®, Percodan®, Tylox®, Vicodin®, Lortab®, Lorcet®, and Tylenol® with Codeine

  Oxycodone is the opioid ingredient in Percocet, Percodan, and Tylox
- Patients are spared the added potential toxicities of maximal daily doses of ASA or APAP
- Convenient q12h schedule won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
- Patients are less likely to anxiously "clock watch" when pain is controlled over long periods

Percodan is a registered trademark of The DuPont Merck Pharmaceutical Co. Tylox is a registered trademark of McNeil Pharmaceutical. Lortab is a registered trademark of Whitby Pharmaceuticals Inc. Lorcet is a registered trademark of UAD Laboratories.

New q12h
OXYCONTIN® (II)
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
Warning—May be habit forming

The one to start with (A-T-C)

For patients with moderate to severe pain requiring opioid therapy for more than a few days

OxyContin™

THE ONE TO START WITH (A-T-C).

Analgesic onset within 1 hour in most patients.

1 hour

— Analgesic onset within 1 hour plus a longer duration of action than Percocet®, Vicodin®, or Tylenol® with Codeine

Percent of patients experiencing analgesic onset.

90%

From a single-dose study.*

*Sunshine A. Onset, peak, and duration of analgesic effect using the sorting technique: a comparison of controlled-release oxycodone v. immediate release oxycodone alone and in combination with acetaminophen. *American Pain Society Program Book.* 1994; A-36, #94607 [Abstract].

OxyContin clinically studied in various pain syndromes

— More than 10 clinical trials
— More than 700 patients with either cancer or noncancer pain
— 100% of patients receiving OxyContin were dosed q12h

In a placebo-controlled, fixed-dose trial in 133 osteoarthritis patients†...

— Prompt reduction in pain intensity occurred within the first 24 hours
— By Day 3, patients had achieved 94% of their total pain reduction
— In this study, OxyContin 20 mg q12h...
  - Significantly decreased pain
  - Improved quality of life, mood and sleep
— 100% of OxyContin patients were dosed q12h

† Roth S, Burch F, Fleischmann R, et al. The effect of controlled-release (CR) oxycodone on pain intensity and activities in patients with pain secondary to osteoarthritis. Presented at the American Pain Society, November, 1995, Los Angeles, CA. Patients entering the study on NSAIDs remained on them throughout the trial.

Please see professional prescribing information on last pages.

New q12h
OXYCONTIN®
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
Warning—May be habit forming

For patients with moderate to severe pain requiring opioid therapy for more than a few days

OxyContin™

THE ONE TO STAY WITH.

The one to stay with

Easy to titrate:

Steady-state blood levels achieved in 24-36 hours.

From a repeated-dose bioavailability study.*

No ceiling to analgesic efficacy.

— With full agonists, such as oxycodone,† effectiveness with increasing doses is not limited by a "ceiling."†‡

— OxyContin can be titrated upward when clinically necessary

***In cancer studies*‡...**

— Titration enhanced efficacy of therapy—only 3.5% of cancer patients discontinued [due to inadequate pain control] when allowed to titrate and use rescue medication

— Patients were titrated as quickly and easily with OxyContin as with immediate-release oxycodone

— 92% of patients were titrated to stable pain control with OxyContin

— Average time to stable pain control was 2 days

— 100% of OxyContin patients were dosed q12h

* Roder R, Kaiko R, Grandy R, et al. Steady-state bioavailability comparison of controlled release oxycodone [OxyContin] tablets vs. oxycodone oral liquid. *American Pain Society Program Book.* 1994; A-36, #94604 (Abstract).

† *Management of Cancer Pain: Adults. Clinical Practice Guideline.* Quick Reference Guide for Clinicians. Rockville, Md: US Dept of Health and Human Services AHCPR publication 94-0593. Public Health Service, Agency for Health Care Policy and Research; March 1994.

‡ Data on file, Purdue Pharma L.P.

Please see professional prescribing information on last pages.

New q12h

OXYCONTIN®

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

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For patients with moderate to severe pain requiring opioid therapy for more than a few days

OxyContin™

EASY TO LIVE WITH.

Common opioid side effects...

Adverse experiences reported over time by cancer patients (n=86)*

Drug-related ADE	Week 1 (%)†	Week 5 (%)†	Week 10 (%)†
Nausea	20	12	4
Sedation	14	8	8
Dry Mouth	9	0	0
Vomiting	8	7	0
Pruritus	7	0	0
Dizziness	5	5	0

*Percent of patients reporting ADE once or more during specified week of OxyContin therapy.

Many diminish over time, except for constipation.

- The most serious risk associated with opioids is respiratory depression
- A significant decrease in the percent of patients reporting adverse events was seen between the first and last weeks of the study ($P<0.0001$)
- Most side effects diminished over time, except for constipation, even as daily doses increased
- Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness

†Kaplan R, Parris W, Croghan M, et al. Decrease in opioid-related adverse experiences (AE) during chronic therapy with controlled release oxycodone (OxyCR) in cancer pain patients. Presented at the American Pain Society, November, 1995, Los Angeles, CA.

Easy to live with

New q12h

OXYCONTIN® (OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

Please see professional prescribing information on last pages.

For patients with moderate to severe pain requiring opioid therapy for more than a few days

OxyContin™ EASY TO DOSE.

Starting on OxyContin.

Recommended initial dose for opioid-naive patients.

For around-the-clock pain:	For supplemental analgesia:
OxyContin™ CII	**Immediate-Release (IR) Oxycodone***
10 mg q12h If a nonopioid analgesic is being taken, it may be continued.	5 mg administered 1 hour before anticipated incident pain 5 mg administered for breakthrough pain (if needed)
Warning: Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. See WARNINGS and PRECAUTIONS Sections in professional prescribing information.	**Note:** If more than two rescue doses are needed per day, OxyContin should be titrated upward.

* See professional prescribing information for immediate-release oxycodone.

Please see professional prescribing information on last pages.

Converting to OxyContin.

Fixed-Combination Opioid/ Nonopioid Products → OxyContin		
Dose of regular-strength products (eg, Percocet®, Percodan®, Tylox®, Vicodin®, Lortab®, Lorcet®, and Tylenol® with Codeine)	**Recommended OxyContin conversion dose range**	**IR oxycodone rescue dose for breakthrough pain***
1-5 Tablets/Capsules/ Caplets per day	10-20 mg q12h	5 mg
6-9 Tablets/Capsules/ Caplets per day	20-30 mg q12h	5-10 mg
10-12 Tablets/Capsules/ Caplets per day	30-40 mg q12h	10 mg

Note: The nonopioid ingredient may be continued as a separate drug. Discontinue all other around-the-clock opioids when initiating OxyContin therapy.

New q12h
OXYCONTIN® CII
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
Warning—*May be habit forming*

For patients with moderate to severe pain requiring opioid therapy for more than a few days

OxyContin® EASY TO DOSE.

The goal of titration:

To effectively control pain with two or fewer rescue doses per day.

OxyContin Titration Guide

	OxyContin Tablets q12h dose	IR oxycodone dose for rescue*	
10mg	10 mg q12h	5 mg	Titrate the OxyContin dose if more than two rescue doses per day are needed.
	20 mg q12h	5 mg	
	30 mg q12h	10 mg	
20mg	40 mg q12h	10 mg	
	60 mg q12h	15 mg	
40mg	80 mg q12h	20 mg	
	120 mg q12h	30 mg	
Continue titrating, if necessary, using the T•I•M•E principles on next page.			

*See professional prescribing information for immediate-release oxycodone.

T itrate patients every 1-2 days, if necessary.

I ncrease the dose by 25%-50%, if necessary†; do not increase the dosing frequency.

M anage breakthrough pain with IR oxycodone* at ¼ to ½ of the 12-hour OxyContin dose.†

E levate the OxyContin dose if more than two rescue doses are required per day.

†For patients taking OxyContin 10mg q12h...

- The next titration step should be 20mg q12h
- Breakthrough pain should be managed with IR oxycodone 5mg

Please see professional prescribing information on last pages.

New q12h
OXYCONTIN® (II)
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
Warning—May be habit forming

Easy to dose

For patients with moderate to severe pain requiring opioid therapy for more than a few days

New q12h

OxyContin® (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Warning: May be habit forming

The one to start with (A-T-C).*
The one to stay with.
Easy to live with.
Easy to dose.

10mg 20mg 40mg

Small, color-coded tablets (actual size)

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

OxyContin™
The longest-lasting oxycodone ever.

*Around-the-clock.

Please see professional prescribing information on preceding pages.

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